CAP REPORT

NUMBER 8

Drugs and the Third World:

Aminophenazone and Dipyrone Hazards and Marketing Practices

CONSUMERS' ASSOCIATION OF PENANG

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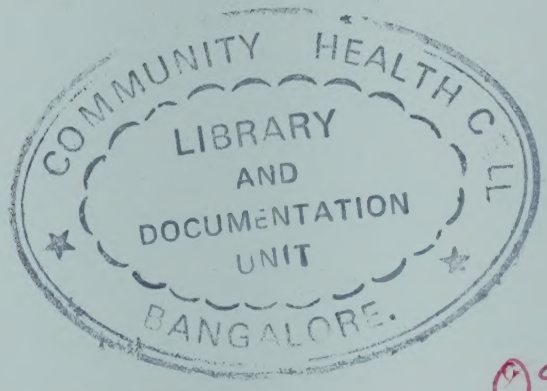
The Consumers' Association of Penang is a voluntary non-profit organisation which fights for the rights and interests of all consumers through research, educational and representational activities.



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PREFACE

Aminophenazone and Dipyrone are two extremely toxic painkilling drugs with a wide range of side effects that include fatal agranulocytosis (severe blood disorder caused by reduction in white blood cell production). Despite their known adverse side effects, however, the drugs are still available and widely used in Malaysia.

The aim of this report by the Consumers' Association of Penang is to show how, because of the lack of effective health regulations and unethical promotion by pharmaceutical companies, the two drugs have been indiscriminately used, leading to great suffering and even deaths among the users.

That Aminophenazone can cause agranulocytosis was first established in 1933. Since then, there has been more evidence of the toxicity of the drug. In 1935, the *Lancet* reported 70 fatal cases of Aminophenazone-induced agranulocytosis, the victims of which died long, lingering deaths. In the same year, evidence showed that over 90% of all cases of agranulocytosis reported in the *Journal of the American Medical Association (JAMA)* over the previous four years had been associated with Aminophenazone. The AMA Registry of Adverse Reactions also recorded 45 cases of agranulocytosis presumed or known to be due to Aminophenazone

between 1957-66. In the 1970s, surveys in Finland showed that about 50% of the cases of agranulocytosis ended fatally, with children being as vulnerable as adults.

As a result of these adverse reports, the use of Aminophenazone was greatly reduced, while Dipyrone became more popular. It was noticed, however, that the increasing popularity of Dipyrone coincided with a rise in the number of cases of agranulocytosis.

Hence, it was proved that Dipyrone and Aminophenazone are equally dangerous and can give rise to the same adverse side effects.

This report points out that many countries have recognised the extreme dangers of the two drugs and taken steps to ban or severely restrict their sale/use. Among these countries are the USA, UK, Japan, Italy, Sweden, Australia, France, West Germany and Singapore.

The World Health Organisation (WHO) has also recommended the complete withdrawal of Aminophenazone, and neither it nor Dipyrone is included in the Organisation's Essential Drugs List.

In Malaysia, however, Aminophenazone and Dipyrone continue to be used. Under the Poisons Ordinance 1952 and the Poisons List 1983, the drugs are classified as Group B Poisons, meaning that they should by right be dispensed only by registered medical practitioners on prescription. However it is a fact that many branded preparations containing these drugs can easily be obtained over the counter in pharmacies and drugstores.

As indicated in this report, such a situation exists because of the inadequate control by the Ministry of Health, thus enabling the pharmaceutical companies to adopt double standards in marketing their drug preparations and to provide insufficient information on their products. Even when they have stopped marketing the drugs in their own countries or in other developed countries, or have reformulated their preparations, the multinational pharmaceutical companies continue to push the original preparations containing the dangerous drugs in Third World countries.

Moreover, they often do not give enough information about the dangers of the drugs and their adverse side effects, nor warnings against their use. Instead, they recommend the drugs for the treatment of a wide variety of ailments, including colds, fever and stomachache. These conditions are minor ones which certainly do not warrant treatment with such potent agents. Some of the preparations are even recommended for use in children. This is highly risky, in view of the extreme toxicity and adverse side effects of the drugs.

In Malaysia, information that is provided by the pharmaceutical companies about their drug preparations is usually incomplete and sometimes misleading, and invariably plays down the dangers of the drugs. The information comes from three sources : the *Drug Index for Malaysia and Singapore (DIMS)*, which is given free to doctors; advertisements and brochures, also prepared by the drug companies; and drug inserts that come together with the drugs purchased. It has been found that, often, the drug inserts are worded in such a way as to imply that self-medication of the

drugs is allowed or even encouraged.

There is reason to believe that because of the inadequate information supplied, many doctors themselves may be prescribing the drugs for their patients with minor complaints such as coughs, headache and menstrual pains, without being aware of the possible dire consequences.

Misuse of the drugs is so widespread that, according to a pharmacologist at the University Hospital, they are among the five drugs responsible for the majority of the adverse drug reactions suffered by patients admitted to the hospital.

Case studies of patients who suffered from adverse reactions to the drugs are provided in this report. One case took place in Mozambique, where an English school teacher almost died after taking CIBALGIN, a preparation containing Aminophenazone. Malaysian cases include two children who died after being administered BONPYRIN (containing Dipyrone). These and other cases have moved a paediatrician into saying, 'BONPYRIN should be banned from the face of this earth.'

In the light of all the facts highlighted in this study, there is no justification for the continued use of Aminophenazone and Dipyrone, especially since other less dangerous and equally effective anti-inflammatory analgesics are available. Aminophenazone and Dipyrone have been shown to be lethal and unpredictable, with no real advantage over safer alternative drugs.

CAP therefore strongly urges the Ministry of Health to act immediately to ban Aminophenazone and Dipyrone, so as to safeguard the health of all Malaysian consumers.

I would like to acknowledge Evelyne Hong for the substantial research and writing of this report, Yap Bing Nyi for editing it, as well as Lim Jee Yuan and Jessie Chan for the production.

S M Mohd Idris, JP
President
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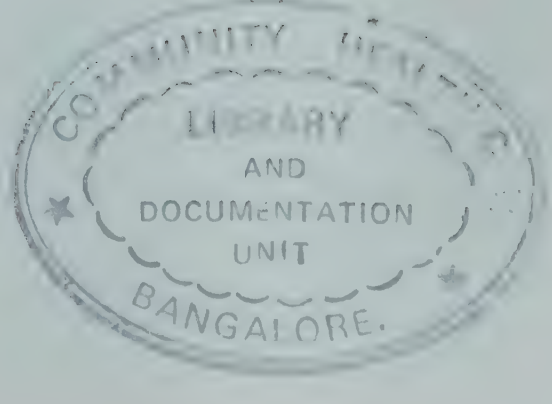
1986



CHAPTER 1

INTRODUCTION

Dipyrone (or Noramidopyrine) and Amidopyrine (or Aminophenazone) are chemically related drugs. Dipyrone is the sodium sulphonate of Amidopyrine and both drugs share similar properties (Martindale 1982:251). They are two painkiller drugs which are known for their potential fatal bone marrow toxicity, agranulocytosis. Evidence has also appeared to suggest that Aminophenazone either by itself or in combination with the nitrites in some foods might cause cancer.

Despite the known dangers, WHO says that 'both aminophenazone and noramidopyrine are still sold direct to the public in many countries, frequently in the form of combination products advertised without warning for relatively trivial symptoms such as headache and toothache. It is probable that several hundred different branded products remain available, and the difficulty of identifying them is compounded by the confusing variety of official names used to describe these two substances' (WHO Drug Information Jan-March 1977:10).

Both the drugs have virtually disappeared from the therapeutic scene in the United States and in Europe. To date, Aminophenazone

has been banned or withdrawn in at least 21 countries including Singapore. Dipyrone has been withdrawn or banned in at least nine countries including Singapore and severely restricted in others. Yet in Malaysia both the drugs continue to be used.

This report by the Consumers' Association of Penang urges the Ministry of Health to immediately review the benefit of these drugs, bearing in mind the deleterious effects of the drugs and hence their toxicity, and to impose a total ban on their use. At present the two drugs are listed as Group B Poisons, which means that according to the law, these drugs can be dispensed only by a medical practitioner on prescription. However, both drugs can be obtained over the counter and are marketed for a wide variety of minor ailments, which should not be the case because of their potential, irreversible and dangerous side-effects and toxicity.

Given the evidence collected in this report, CAP urges the Ministry of Health to ban the sale of Dipyrone and Amidopyrine in Malaysia.

CHAPTER 2

AMINOPHENAZONE: INN (International Nonproprietary Name Selected By WHO)

Other Generic Names:

Amidophenazone	Amidopyrazoline	Dipyrin
Aminopyrine	Amidofebrin	Pyramidon
Amidopyrine		

Aminophenazone comes under the Pyrazolone derivatives which also include Phenylbutazone, Oxyphenbutazone, Dipyrone, Antipyrene and Apazone (Goodman and Gilman's 6th Edition:698).

Aminophenazone was introduced in the late nineteenth century as an antipyretic (Goodman and Gilman's 6th Edition:701); and it has been used for its potent anti-inflammatory and analgesic action for more than 70 years, although Aminophenazone-induced agranulocytosis (severe depression of infection-battling white blood cell production) was not established until 1933 (WHO Drug Information Jan-March 1977:9).

(1) Actions

It is the most effective of the antipyretic analgesics with a potent anti-inflammatory effect. However, due to its potential

fatal bone-marrow toxicity, agranulocytosis, the use of this drug has been discouraged (Martindale 1982:245).

(2) Adverse Effects of the Drug

According to *Meyler's Side Effects of Drugs, 90th Edition:* 'Amidopyrine is probably the most dangerous of all anti-inflammatory analgesics. The development of blood dyscrasias after therapeutic doses has been well documented in hundreds of cases.'

'Agranulocytosis seems to be an allergic manifestation, requiring initial sensitization followed after weeks, months, or even years by re-exposure to the drug' (Discombe 1952: 1271-3).

'There is no doubt that Amidopyrine has repeatedly been responsible for bone-marrow depression and the death of patients .... There is no indication why Amidopyrine should not be replaced by other analgesic or anti-inflammatory drugs, ...' (Meyler's 1980:146).

'A wide variety of blood dyscrasias (diseases) have appeared 1 - 2 weeks after the beginning of Amidopyrine treatment. Severe bone-marrow depression has usually been characterized by a fulminant, very severe clinical course and can progress to death despite immediate and intensive treatment' (Ibid).

Amidopyrine can cause a great number of allergic skin reactions even after very brief treatment. Toxic epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson Syndrome and acute

anaphylactic shock have all been observed (Ibid).

According to *Martindale, Twenty Eighth Edition,* 'The risk of agranulocytosis in patients taking Amidopyrine is sufficiently great to render this drug unsuitable for use. Onset of agranulocytosis may be sudden and unpredictable' (Martindale 1982: 245).

The Clinical Toxicology of Commercial Products, Fourth Edition lists Amidopyrine as very toxic or number 4 in its Toxicity Rating. It states that 'Most of the toxicity reported for this drug seems to be due to hypersensitivity, notably ... fatal agranulocytosis and angioneurotic edema (swelling of the whole body)' (Clinical Toxicology 1976:239).

On drug-induced agranulocytosis, D. R. Laurence in his book *Clinical Pharmacology* states that 'Amidopyrine is notorious in this respect and need never be used, as there are adequate substitutes' (Laurence 1973:6.60).

It can also cause acute brochospasm in asthmatic patients which can be fatal (Meyler's 1980:146).

Chronic gastritis has developed after long-term abuse of combined preparations containing Amidopyrine (Ibid:146).

Liver damage has also been reported accompanied by a general hypersensitivity reaction (Ibid:146).

Amidopyrine has a direct nephrotoxic effect. Albuminuria, haematuria and acute renal failure have all been reported after therapeutic dosage or overdosage. Amidopyrine can also contribute to the development of analgesic nephropathy (Ibid:147).

There is a possibility of Amidopyrine (and its derivatives) undergoing conversion to carcinogenic nitrosamine compounds (Ibid:147). Toxicological studies in 1972 have shown it to be a potential carcinogen as it can react with nitrites in the stomach of animals to produce Dimethylnitrosamine (Lijinsky, W., and M. Greenblatt 1972:177-8; Sander, J., and F. Schweinsburg 1972:299-340). In rats this interaction led to the formation of malignant tumours in the liver and lungs (Lijinsky, W., et al, 1973:176-8). Dimethylnitrosamine was also catalysed by Thiocyanate present in the saliva particularly in smokers (Boyland, E., and S. A. Walker 1974:1181).

(3) Studies on Aminophenazone

Table I: Reports on Agranulocytosis due to Amidopyrine

Country	Year	No./Percentage of Cases	No./Percentage of Fatalities	Rate of Incidence of Reaction
UK	1935		70	
US	1935	90%		
UK	1951			1.1%
UK	1952			0.8%
US	1957-66	45		
Finland	1970s		50%	0.00001%

Sources: *WHO Drug Information* Jan-March 1977: 9-11; *Martindale* 1982: 245; *British Medical Journal* 1952: 1271-3

(a) In 1935 a *Lancet* report cited 70 fatal cases of Amidopyrine-induced agranulocytosis (the victims died long, lingering deaths) (Plum, P 1935: 14-21).

(b) In another study reported in the *Journal of the American Medical Association (JAMA)* in 1935, evidence showed that over 90% of all cases of agranulocytosis reported in the medical literature over the previous four years had been associated with Amidopyrine (Kracke, R.R., and F.P. Parker, 1935:960-6).

(c) In the UK, the incidence of Amidopyrine-induced agranulocytosis during 1951-2 was 0.8-1.1% (Lancet 1/1951:389; Discombe, G., 1/1952:1270; Hartl, P.W., 1973:147).

(d) The American Medical Association (AMA) Registry of Adverse Reactions recorded 45 cases of agranulocytosis presumed or known to be due to Amidopyrine and 25 in which another drug might have been involved in the period 1957-66 (Med. Lett. 1973: 4, 15).

(e) Comprehensive surveys in Finland in the early 1970s show that although the frequency of the reaction was calculated as 1:100,000, approximately 50% of the cases ended fatally and children were shown to be as vulnerable as adults (Palva, I.P., Mustala, O.O., 1970:109-15; Kantero, I., Mustala, O.O., and Palva, I.P., 1972:327-30).

It is clear that Aminophenazone is an extremely dangerous drug, with numerous adverse side effects that include fatal agranulo-

cytosis. Therefore the drug should not be used, especially when safer, alternative drugs are available for the treatment of a certain complaint.

CHAPTER 3

DIPYRONE: INN

Other Generic Names:

Noramidopyrine	Methampyrone
Metamizol	Sulpyrine

Since Aminopyrine fell into disrepute some of its derivatives, including Dipyrone, have been promoted (Huguley 1964: 938-41).

Dipyrone is the sodium sulphonate of Amidopyrine and has similar properties (Martindale 1982: 251). Dipyrone is also marketed by various manufacturers under different names like Metamizol, Noramidopyrine and Sulpyrine. Hoechst patented their original research product Metamizol in 1911. This multiplicity of names has to some extent confused physicians leading them to believe that Dipyrone and the notorious Aminopyrine were quite different (Silverman, Lee and Lydecker 1982: 63).

The use of Dipyrone to replace Aminophenazone caused great concern to the American Medical Association. In the 1973 edition of the ***AMA*** *Drug Evaluations,* American physicians were warned that:

> 'There is evidence that Dipyrone, a derivative of Aminopyrine that shares its potential for toxicity, unfortunately is still being misused. This is probably because it is available in injectable form and because

> physicians do not recognise its similarity to Aminopyrine since it is marketed under various trademarks .... Its only justifiable use is as a last resort to reduce fever when safer measures have failed .... Because Dipyrone may produce fatal agranulocytosis and other blood dyscrasias, its use as a general analgesic, antiarthritic, or routine antipyretic cannot be condoned' (AMA Drug Evaluations 1973: 262, 267).

According to *Meyler's Side Effects of Drugs, 90th Edition,* 'The main derivatives of Amidopyrine can provoke the same spectrum of adverse reactions as Amidopyrine itself .... both Amidopyrine and its derivatives are dangerous in the same way and to the same extent' (Meylers 1980: 147).

In the early 1960s, the increasing popularity of Dipyrone (Metamizol) was matched by a rise in reports of drug-related agranulocytosis (WHO Drug Information Jan-March 1977: 9). This was after the use of Amidopyrine was greatly reduced when it was recognised that the drug was associated with agranulocytosis (Ibid). The first case of agranulocytosis associated with Dipyrone was reported in 1935 (Huguley, C.M. 1964: 938-41). In 1964 an article in *JAMA* commented that the 'recent increase in the use of Dipyrone and in cases of agranulocytosis and death resulting from it must give us pause, particularly since so many children are among the victims' (Ibid).

The Philippine Paediatric Society has been warning paediatricians that Dipyrone is highly protein bound, as such it takes at least 15 - 20 minutes to take effect even after intramuscular injection (Ang Mamimili 1979 Vol VII No. 11: 166-7).

This means that it stays in the body longer, hence detoxification is delayed and this condition is very dangerous to children.

(1) Actions

According to *Martindale, Twenty Eighth Edition,* 'The use of Dipyrone is justified only in serious or life-threatening situations where no alternative antipyretic is available or suitable' (Martindale 1982:251).

(2) Adverse Effects of the Drug

According to *Meyler's Side Effects of Drugs, 90th Edition,* 'There can be no doubt that Aminopyrine and Dipyrone cause agranulocytosis ... Since effective, less dangerous alternative drugs are available there is no case for the continued use of Aminopyrine and Dipyrone' (Meyler's 1980:63-4).

According to the *American Medical Association Drug Evaluations, Second Edition,* 'There is evidence that Dipyrone, a derivative of Aminopyrine that shares its potential for toxicity, unfortunately is still being misused. This is probably because it is available in injectable form and because physicians do not recognize its similarity to Aminopyrine since it is marketed under various trademarks.... Because Dipyrone may produce fatal agranulocytosis and other blood dyscrasias, its use as a general analgesic, antiarthritic, or routine antipyretic cannot be condoned' (AMA Drug Evaluations 1973:262, 267).

(3) Drug Interactions

Severe hypothermia (abnormally low body temperature) can result if Dipyrone and Chlorpromazine (a tranquilliser also used to prevent nausea and vomiting) were given concomitantly (Med. Lett. 1973:4, 15).

A mixed preparation containing Phenopyrazone has provoked a systemic lupus erythematodes-like reaction (Meyler's 1980:147).

(4) Studies on Dipyrone

Table II: Reports on Adverse Reactions to Dipyrone

Country	Year	No of Cases	Type of Reaction	No of Fatalities	Rate of Incidence of Reactions
US	1957-66	40	Agranulocytosis		
Sweden	1966-70	27	Agranulocytosis	7	
Israel	1973		Skin reactions		24%
US	1976	10	Allergic Reactions		1%
Soviet Union	1980	470	Skin rashes		38%
			Dyspepsia		12%
			Fever		9%
			Anaphylactic shock		7%
			Bronchospasm		4%
			Thrombocytopenia		0.6%
			Leukopenia		0.2%
			Agranulocytosis		0.2%

Sources: *Martindale* 1982: 245,251; Dukes (ed.) 1980: 63-4; *WHO Drug Information* July-Sept 1977: 8-9

(a) The American Medical Association Registry of Adverse Reactions recorded 40 cases of agranulocytosis presumed to be due to Dipyrone and a further 22 possibly due to the drug in the period 1957-66 (Med. Lett., 1973:4, 15).

(b) The Swedish Adverse Drug Reaction Committee for the five-year period 1966-70 showed that agranulocytosis attributed to Dipyrone had been reported on 27 occasions, seven of which were fatal. It was estimated that the reported figures represented one-third of the true frequency (L.E. Bottiger & B. Westerholm 1973:339).

(c) This high reaction rate was also found in another study in Israel in which the incidence of skin reactions to Dipyrone was estimated at 24 per 100 (Levy, M. 1973:167-70).

(d) According to a detailed survey conducted by the Boston Collaborative Drug Surveillance Programme in 1976, of the 876 patients exposed to Dipyrone, 10 developed an allergic reaction (Arndt, K.A., and Jick, H., 1976:918-23).

(e) In a Soviet study of 470 patients given Dipyrone, 'skin rashes occurred in 38%, dyspepsia in 12%, fever in 9%, anaphylactic shock in 7% and bronchospasm in 4%. Thrombocytopenia occurred in three patients, another developed leukopenia and there was a single case of agranulocytosis' (Dukes (ed.) 1980:63-4).

Since Dipyrone is not any safer than Aminophenazone in terms of adverse side effects, its continued use should not be allowed. This is especially true when there are other, safer substitute drugs for the treatment of illnesses.

CHAPTER 4

REGULATIONS CONCERNING AMINOPHENAZONE AND DIPYRONE IN OTHER COUNTRIES

AMINOPHENAZONE

By the late 1930s the dangers of Aminopyrine-induced agranulocytosis became known. By the 1970s severe restrictions on the use of the drug were taken by the US and several countries in Europe. Physicians were told that the drug was 'unsuitable for use' and had 'become obsolete' and clinical use of the drug 'was sharply curtailed'. Many of the manufacturers either withdrew the product or reformulated it to remove Aminopyrine. By 1980 it was even dropped from many physicians' references in Europe and in the US. The World Health Organization has also recommended the complete withdrawal of Aminophenazone and it is not listed in WHO's Essential Drugs List.

Although some Aminopyrine products were replaced by other closely related Pyrazolone derivatives, particularly Propyphenazone, there is still little documented evidence to show that Propyphenazone is any safer (or more dangerous) than Aminopyrine with regard to agranulocytosis. In fact, according to WHO, potentially fatal or permanently disfiguring lesions, including toxic epidermal necrolysis, exfoliative dermatitis and Stevens-Johnson Syndrome, have each been attributed to drugs within this group (WHO Drug Information July-Sept 1977: 8-9).

In Malaysia, under the Poisons Ordinance 1952 and the Poisons List 1983, Aminopyrine and its salts are listed as Group B Poisons. This means that the drug can be dispensed only by a registered medical practitioner on prescription. In many other countries, however, the drug has been totally banned.

Table III: Regulations Concerning Aminophenazone and Dipyrone Worldwide

	Year of Ban/Withdrawal	
	Aminophenazone	Dipyrone
1) Australia	1964	1964
2) Austria	1978	
3) Bangladesh	1982	1982
4) Belgium	1978	
5) Chile	1984	
6) Denmark	1979	1979
7) Finland	1976 (Prescription Control)	
8) France	1982	1980 (Prescription Control)
9) Federal Republic of Germany	1977	1983 (severely restricted)
10) Greece	1980	

Table III: Regulations Concerning Aminophenazone and Dipyrone Worldwide (continued)

	Year of Ban/Withdrawal	
	Aminophenazone	Dipyrone
11) India	1979	
12) Israel		1983 (severely restricted)
13) Italy	1978	1979
14) Japan	1977	1977
15) Kuwait	1979	
16) Nepal	1983	
17) Norway		1976
18) Peru		1982 (Prescription Control)
19) Philippines		1977 (severely restricted)
20) Romania	1982 (gradual reduction)	
21) Rwanda	1983	
22) Saudi Arabia	(withdrawal now under consideration)	1983
23) Singapore	1978	1978

Table III: Regulations Concerning Aminophenazone and Dipyrone Worldwide (continued)

	Year of Ban/Withdrawal	
	Aminophenazone	Dipyrone
24) South Korea	1978	
25) Sweden	1977	1977
26) Switzerland	1977	
27) Turkey	1982	
28) UK	1977	1977
29) US	1977	1977
30) Venezuela	1982	1982
31) Yemen Arab Republic	1980	

Source: *Consolidated List Of Products Whose Consumption And/Or Sale Have Been Banned, Withdrawn, Severely Restricted Or Not Approved By Governments*, Prepared by the United Nations Secretariat in response to General Assembly resolution 37/137 First Issue, 30 December 1983: *WHO Drug Information* - various years.

United States

The FDA withdrew Aminophenazone from over-the-counter sales and placed it under prescription control in 1938. In 1977 the *AMA Drug Evaluations* in the US stated that the drug 'has become obsolete in this country' and it was dropped completely from the 1980 edition (Silverman, Lee and Lydecker 1982:62-3). Although no formal prohibition has been imposed on the sale of the drug in the US, it is no longer available since it is not listed as a constituent of any product currently registered within the country (WHO Drug Information Jan-March 1977:10). It is thus not registered in the US Physicians' Desk Reference 1983.

Australia

Aminopyrine was banned in Australia in 1964 (WHO Drug Information Jan-March 1977:10). Importation is prohibited because of the potential hazard of bone-marrow depression and fatal agranulocytosis (UN Secretariat 1983:10-11).

Sweden

The drug was withdrawn from sale in Sweden in 1977 (Ibid:10).

United Kingdom

The drug has been withdrawn from sale in the UK since 1977 (Ibid:10).

Federal Republic of Germany

Aminophenazone has been withdrawn from all analgesic/antipyretic preparations since 1977 (WHO Drug Information July-Sept 1977:16). In 1982 a Reuter report said that West Germany's Federal Health Office was banning 80 pain-killing and anti-fever drugs containing Pyrazolone suspected of causing blood disorders. A further 212 drugs containing the chemical have had restrictions placed on their use and 649 others will carry written warnings on the packaging. These measures were necessary because of 'well-founded suspicion that in relatively few cases, the frequency of which is disputed, use of these drugs can lead to damage to blood composition and shock conditions' (New Straits Times 16 August 1982).

In 1983, labelling for Pyrazolone-containing drugs which include Noramidopyrine Methanesulfonate Sodium (Dipyrone and Metamizol), Isopropylamino-Phenazone, Nifenazone, Propyphenazone, Phenazone, and Morazone was revised. Indications are now limited to the treatment of acute severe pain - such as post-traumatic and post-operative pain and colic or high fever unresponsive to other therapy. Their use in inflammatory arthroses (inflammatory conditions of the joints) is specifically excluded.

Contraindications include conditions predisposing to shock or bone-marrow depression, known allergy to Pyrazolones and Phenylbutazone, and certain metabolic deficiencies such as hepatic porphyria or bone-marrow depression.

The importance is stressed of weighing the need for treatment against the slight but life-threatening risks of anaphylactic shock and agranulocytosis.

The Federal Health Office has also announced the withdrawal of irrational combination products containing these substances, and those preparations indicated for conditions that are no longer admitted (WHO Drug Information Jan-Dec 1983:29).

Japan

Japan has withdrawn Aminophenazone from all analgesic/antipyretic preparations since 1977 (WHO Drug Information July-Sept 1977:16).

The Central Pharmaceutical Affairs Council in Japan has taken a further step by removing all the pyrazolones (due to their propensity to cause frequent skin eruptions and serious shock) from proprietary cold medicines or antipyretic-analgesic preparations which are available without a doctor's prescription (Japan Medical Gazette 20 June 1977:12). Some of these compounds include Aminopyrine, Dipyrone, Phenazone, Propyphenazone, Aminopropylon and Nifenazone (Ibid).

Italy

Aminophenazone products for oral use were withdrawn in 1978 because of the risk of formation of carcinogenic nitrocompounds. Injectable products require warnings about the risk of hypersensitivity reactions (UN Secretariat 1983:9-11).

Switzerland

Switzerland has withdrawn the drug from all analgesic/antipyretic preparations since 1977 (WHO Drug Information July-Sept 1977:16), because of its potential to produce carcinogenic nitrosamines. Ciba-Geigy and Sandoz voluntarily decided to remove this substance from their products (UN Secretariat 1983:9-11).

Austria

The drug has been withdrawn from Austria since 1978 (WHO Drug Information April-June 1978:19), in view of its propensity to form a potentially carcinogenic N-nitroso compound (UN Secretariat 1983:9-11).

Denmark

At the recommendation of the Registration Board in Denmark, preparations containing Aminophenazone and Noramidopyzone were withdrawn from Denmark in April 1979. The decision was based on the potential danger of bone-marrow depression and fatal agranulocytosis, suspected carcinogenic hazards, and the availability of safer alternative products (WHO Drug Information April-June 1979:13).

Finland

The Finnish authorities have placed Aminophenazone on prescription control owing to the potential hazard of bone-

marrow depression and agranulocytosis, which means that refills will not be permitted (WHO Drug Information Jan-March 1977:10; UN Secretariat 1983:9-11).

Venezuela

Aminophenazone has been withdrawn from Venezuela because of its carcinogenic potential (UN Secretariat 1983:9-11).

Belgium

Both Ciba-Geigy and Sandoz have replaced Aminopyrine with Propyphenazone in the following combination products marketed in Belgium: Cibalgine, Irgapyrine, Optalidon and Spasmo-Cibalgine (WHO Drug Information July-Sept 1978:19).

France

The Committee for Registration of Medicines recommended that all preparations containing Aminophenazone be withdrawn from the market as of 1 January 1982 (WHO Drug Information Oct-Dec 1980:22).

Greece

Aminophenazone was withdrawn from use in October 1980 by the Ministry of Health and Welfare in Greece (UN Secretariat 1983:9-11).

Turkey

The Ministry of Health withdrew the drug and recommended the reformulation of all products containing Aminophenazone in 1982, owing to the potential danger of bone-marrow depression and fatal agranulocytosis and the availability of safer alternative products. Export of this product is prohibited (UN Secretariat 1983:9-11).

Romania

The Minister of Health in Romania recommended the gradual reduction in the use of Aminophenazone in 1982 until it was phased out of use completely (UN Secretariat 1983:9-11).

Yemen Arab Republic

The Supreme Board of Drugs in the Yemen Arab Republic called for the withdrawal of all Aminopyrine preparations from 1 January 1980 (WHO Drug Information Oct-Dec 1979:17).

Kuwait

The drug was banned for use or sale by Ministerial Decree 556/78 because of its dangerous side effects, mainly agranulocytosis, in December 1979 (UN Secretariat 1983:9-11).

Saudi Arabia

The drug is being reviewed and withdrawal is under considera-

tion (UN Secretariat 1983:9-11).

India

Aminopyrine has been withdrawn from India since 1979 (WHO Drug Information Jan-March 1979:13). It is prohibited for manufacture, sale and import owing to questionable therapeutic value, evidence of adverse effects on bone-marrow as well as suspected carcinogenic hazards, and the availability of other safer analgesic drugs (UN Secretariat 1983:9-11).

Republic of Bangladesh

Under The Drugs (Control) Ordinance, 1982, Schedule I, Bangladesh has prohibited the manufacture, import, distribution and sale of Aminophenazone with Phenylbutazone (People's Republic of Bangladesh 12 June 1982).

Nepal

All products containing Amidopyrine have been withdrawn in Nepal since 1983 (WHO Drug Information Jan-Dec 1983:23).

South Korea

The drug has been withdrawn from South Korea since 1978 (WHO Drug Information April-June 1978:19), in view of its propensity to form a potentially carcinogenic N-nitroso compound (UN Secretariat 1983:10-11).

Rwanda

All products containing Aminophenazone have been withdrawn from the market in Rwanda (WHO Drug Information Jan-March 1984:26).

Singapore

Singapore has banned Aminophenazone since 1978.

Chile

The Institute of Public Health in Chile has announced the withdrawal from the market of products containing Aminophenazone, because of its carcinogenic potential (WHO Drug Information July-Sept 1984:29).

DIPYRONE

Under the Malaysian Poisons Ordinance 1952 and the Poisons List 1983, Dipyrone is listed as a Group B Poison. This means that the drug can be dispensed only by a registered medical practitioner on prescription. However, many other countries have put a total ban on the drug. It is also not included in WHO's Essential Drugs List.

Peru

Dipyrone is placed on prescription use and all package and/or drug labels for this product must carry the warning that the drug may cause agranulocytosis (UN Secretariat 1983:131-2).

Venezuela

Dipyrone is not approved for use or sale in Venezuela (UN Secretariat 1983:131-2).

Australia

Dipyrone was banned in Australia in 1964 (WHO Drug Information Jan-March 1977:10).

Sweden

Dipyrone has been withdrawn from sale in Sweden since 1977 (WHO Drug Information Jan-March 1977:10), in view of adverse reactions that are in disproportion to the drug's benefits. Dipyrone is not produced in Sweden (UN Secretariat 1983:131-2).

Norway

The drug was withdrawn from the market in 1976 (UN Secretariat 1983:131-2).

Denmark

Dipyrone preparations were withdrawn in Denmark in April 1979. The decision was based on the potential danger of bone-marrow depression and fatal agranulocytosis, and the availability of safer alternative products (WHO Drug Information April-June 1979:13).

United Kingdom

The drug has been withdrawn from the United Kingdom since 1977 (WHO Drug Information Jan-March 1977:10).

Italy

Since 1979, Italy has withdrawn all Dipyrone preparations for intravenous injection and intramuscular injection that contain more than 1 gramme per vial (WHO Drug Information Oct-Dec 1979: 17). Intravenous preparations in combination with other compounds have been withdrawn. The label for marketed preparations carries a warning regarding fatal accidents due to hypersensitivity (UN Secretariat 1983: 131-2).

United States

The US FDA withdrew Dipyrone in 1977 on the grounds that 'the incidence and risk of potentially fatal agranulocytosis ... far outweigh any benefit that can be derived from its use' (WHO Drug Information Jan-March 1977:10). It has not been registered in the US Physicians' Desk Reference since 1983.

France

The Committee for Registration of Medicines in France has placed all preparations containing Dipyrone under strict prescription control which means that refills will not be permitted (WHO Drug Information Oct-Dec 1980:22).

Saudi Arabia

Owing to several reports of anaphylactic shock, the drug has been prohibited for intravenous and intramuscular injections as of December 1983 (UN Secretariat 1983:131-2).

Israel

The use of Dipyrone has been restricted to the management of severe pain in hospitalized patients only. Close clinical and laboratory monitoring is recommended and intravenous use of parenteral preparations is contraindicated (WHO Drug Information Jan-Dec 1983:27).

Republic of Bangladesh

Under The Drugs (Control) Ordinance, 1982, Bangladesh has prohibited the manufacture, import, distribution and sale of Dipyrone. However, the NOVALCIN brand of Dipyrone ampoule is placed on the Restricted List and can be prescribed only by specialists (People's Republic of Bangladesh 12 June 1982).

Philippines

The Food and Drug Administration of the Department of Health under the Administrative Order No. 330 Series of 1977 has stipulated that Dipyrone is a restricted drug in the Philippines, used only as a last resort in serious and life-threatening situations when other less toxic, antipyretic drugs and other measures have failed (Ang Mamimili May 1978 Vol VII No. 5:81).

All use of Dipyrone has been banned at the Philippines General Hospital except for terminal cancer patients (Ang Mamimili 1979 Vol VII No. 11:166-7). The package inserts are required to carry extensive warning information, especially regarding the risk of fatal agranulocytosis. The drug is available only on prescription (UN Secretariat 1983:131-2).

Japan

In May 1977, Japan removed Dipyrone from all proprietary cold medicines or antipyretic-analgesic preparations available without a doctor's prescription (WHO Drug Information July-Sept 1977:8). In 1984, Takeda, the largest Japanese pharmaceutical company, informed its subsidiaries in Southeast Asia to stop selling its Dipyrone cold remedy BENZA D. Takeda has also stopped its production of Dipyrone injection preparation BONPYRIN in Japan (ICADIS News No. 8, June 1984).

Singapore

Singapore has banned all preparations containing Dipyrone since 1978.

It can be seen that while many other countries have totally banned the use or sale of Aminophenazone and Dipyrone, both the drugs are still available in Malaysia. Except for the condition that the drugs must be prescribed by a registered medical practitioner, there are no other restrictions on their use.

CHAPTER 5

INTERNATIONAL MARKETING OF AMINOPHENAZONE AND DIPYRONE

Despite the action taken by several countries on Amidopyrine and Dipyrone, a reminder in the WHO report is apt here: The drugs continue to be 'sold direct to the public in many countries, frequently in the form of combination products advertised without warning for relatively trivial symptoms such as headache and toothache. It is probable that several hundred different branded products remain available, and the difficulty of identifying them is compounded by the confusing variety of official names used to describe these two substances' (WHO Drug Information Jan-March 1977:10).

This is especially true in the Third World, as investigations by Silverman, Lee and Lydecker of the US Institute of Health Policy Studies, University of California, have shown. According to them Aminopyrine preparations which do not carry any warning against agranulocytosis continue to be marketed in Indonesia and Central America. In Central America the reference book lists Ciba-Geigy's brand product ESPASMA-CIBALGINA and the products of two Spanish firms, Liade's HEMICRANEAL and Lacer's MELOKA. Ciba-Geigy and Liade do not give specific warning about agranulocytosis in their products while Lacer does not state warnings of any kind of theirs (Silverman, Lee

and Lydecker 1982:63).

In 1974, Robert Ledogar, a consultant to the Consumers Union in the US, found that many US multinationals were marketing Dipyrone in Latin America for the treatment of minor ailments. The multinationals included Endo, a subsidiary of DuPont, which marketed VALPIRONE; ICN, which marketed GENSERVET; McKesson, a unit of Foremost-McKesson, which marketed DIPIRONA MK; Merrell, a division of Richardson-Merrell, which marketed CORICIDIN S/A and CORILIN children's suppositories; Searle, which marketed STEGALGINA; and Upjohn, which marketed ALGI-NODIA. Checking with the FDA, he was told that none of these companies marketed Dipyrone in the US (Ledogar 1975:33).

In September 1974, Ledogar found that in the Dominican Republic, NOVALDIN (marketed by Winthrop, a division of Sterling Drug) advertisements which appeared in 1974 in *Archivos Dominicanos de Pediatria,* a professional journal for pediatricians, showed a '"contented child" and "happy mother" smiling over the "agreeable flavour" of NOVALDIN drops for children', and 'No warnings were given in these advertisements' (Ledogar 1975:32).

Earlier in March and April 1974, Ledogar purchased Winthrop's CONMEL brand of Dipyrone in Brazil 'in individual cellophane packets marked "Analgesic, Antithermic, Antirheumatic" which were recommended for "migrane, headaches, neuralgia, muscular or articular rheumatism, hepatic and renal colic: Pain and fever which usually accompany grippe, angina, otitis, and sinusitis. Toothaches and pain after dental extractions" '

(Ibid:32).

Further, he found that the Brazilian *Index Terapeutico Moderno*, which is an index of pharmaceutical preparations based on information supplied by the drug companies and distributed free to all Brazilian doctors, recommended CONMEL for the 'symptomatic treatment of all diseases characterized by fever and acute pain, including grippe, colds, pneumonia, and other infectious illnesses' (Ibid:33).

CONMEL is described in the Index as 'an indispensable supplement in the initial and continuing treatment of the very varied minor ailments which constitute a good portion of medical practice. In daily practice many opportunities to prescribe CONMEL will be found' (Ibid:33). According to Ledogar CONMEL was the more popular brand of Dipyrone marketed in Latin America and in 1972 CONMEL was number 20 on the list of best-selling ethical drugs in Colombia (Ibid:33).

Winthrop also markets combination products containing Dipyrone, such as BESEROL and DOLOPIRONA, in many Latin American countries (Ibid:33). In February 1974, Ledogar discovered an advertisement for BESEROL 500 (containing Dipyrone and a muscle relaxant) which appeared in *Ginecologia Y Obstetricia de Mexico* recommending the product ' "for menstrual pain" and proclaiming 93.5% "excellent results" ' although in the US, FDA-required drug labelling had warned women who were menstruating against using Dipyrone because of the possibility of severe haemorrhage (Ibid:41).

The continued marketing of the CONMEL and BESEROL brands of Dipyrone by Sterling Drug in the Third World has caused growing concern among its shareholders. In May 1984, Church shareholders of Sterling Drug filed a resolution at the Sterling Drug annual shareholders' meeting asking the company to consider reformulating CONMEL and BESEROL, replacing Dipyrone with a safer analgesic. Father John Gietner of the Maryknoll fathers, who are shareholders, said at the meeting that 'Sterling has not shown any willingness to monitor the users of Dipyrone. Given the hazards of the drug, we do not think it is responsible for the company to continue to market Dipyrone without being able to monitor its side effects. This is simply unfeasible in the Third World where many people have no access to doctors, let alone sophisticated laboratory facilities. We are therefore asking for an urgent reappraisal by the company, of its positions.'

The Church Shareholders' Resolution also stated that whereas a number of major US drug companies (including Schering Plough, Warner Lambert, American Cyanamid, SmithKline Beckman, American Home Products and Foremost McKesson) which previously marketed Dipyrone have stopped manufacturing, or have reformulated their Dipyrone drugs, 'CONMEL and BESEROL can be bought over the counter in pharmacies and even grocery stores without a prescription in the Third World'.

When Silverman and Lydecker carried out their on-the-spot investigation in Third World countries in 1980-1, they also found Dipyrone products widely used or promoted, and recommended for all kinds of pain from 'headache, rheumatic and

arthritic pain, lumbago, and neuralgia to toothache and menstrual discomfort. Some are advocated to relieve the inflammation of arthritis' (Silverman, Lee & Lydecker 1982:64).

They also found inconsistencies in the labelling of Dipyrone products. The US Winthrop group including Sterling-Winthrop and Winthrop-Stearns, West Germany's E Merck and Hoechst and Japan's Tanabe companies, which market essentially the same products, carry warnings of agranulocytosis in some Third World countries but not in others (Ibid: 64).

For example, CONMEL in Indonesia and Malaysia does not carry warnings against agranulocytosis whereas in Africa and the Philippines it does. In Central America CONMEL carries a 'sensitivity' warning; the word may or may not indicate a hypersensitivity involved in causing blood damage (Ibid:64-7).

There are therefore double standards and inconsistencies in the marketing of Aminophenazone and Dipyrone, especially in the Third World. Often, not enough information (if any at all) is given about the dangers of the drugs, which may obtained over the counter without a prescription and which are recommended for even minor ailments.

CHAPTER 6

DRUG INFORMATION AND BRANDS SOLD IN MALAYSIA

In Malaysia, doctors obtain information on Aminophenazone and Dipyrone from three major sources. They are:

(a) *The Drug Index for Malaysia and Singapore (DIMS)*. *DIMS* is a quarterly publication on ethical medicines available in Malaysia and Singapore. It is prepared by the pharmaceutical companies and distributed free to doctors in both countries.

(b) Drug advertisements and brochures which are distributed free to doctors by drug company retailmen.

(c) Drug inserts which come together with the drugs purchased. The insert gives information on the use of the drug, its dangers and the precautions to be taken. The instructions and information on the drug insert are provided by the company which markets its particular brand product.

In Chapters 7-11 we will examine information from these three sources which are provided to doctors in Malaysia. The information was obtained by referring to *DIMS*; by examining some advertisements which appear in *DIMS* and journals like *The*

Family Practitioner and brochures published by the drug companies; and finally by examining the package inserts of the various Aminophenazone and Dipyrone products. In general, it was found that the information regarding both drugs provided by the pharmaceutical industry was inadequate and in some cases found to be misleading. Some of the preparations also contained other lethal painkillers in combination.

DIMS Vol 14 No 3 October 1985 lists 15 Aminophenazone and Dipyrone preparations. All 15 preparations are Group B Poisons which means that according to the law, these drugs can be dispensed only by a medical practitioner on prescription.

The contents of the various Aminophenazone and Dipyrone preparations, together with their manufacturers, are listed in Table IV. These companies include: Hoechst (FRG); Asta Werke (FRG); Weber (FRG); Merck (FRG); Organon (USA); Winthrop (USA); Takeda and Daiichi Seiyaku (Japan).

TABLE IV: Aminophenazone and Dipyrone Preparations Available in Malaysia

Source: *DIMS* October 1985

	BRAND NAME	MANUFACTURER	CONTENTS	
1.	AMIZONE	Weber	Phenylbutazone sod	150 mg
			Amidopyrine	150 mg
			Lidocaine HCL	10 mg

	BRAND NAME	MANUFACTURER	CONTENTS (continued)	
2.	RHEUMOPYRINE	Ciech Polfa	Phenylbutazone	125 mg
			Amidopyrine	125 mg
3.	AVAFORTAN (Old Formula)	Asta-Werke	Injection : per 2 ml ampoule	
			Avapyrazon	24 mg
			Noramidazophen	240 mg
4.	BARALGIN	Hoechst	Injection : per 10 ml ampoule	
			Metamizol	500 mg
			Pitofenone HCL	2 mg
			Fenpiverinium bromide	0.02 mg
			Tablet :	
			Metamizol	500 mg
			Pitofenone	5 mg
			Fenpiverinium bromide	1 mg
			Dragee :	
			Metamizol	250 mg
			Pitofenone	2.5 mg
			Fenpiverinium bromide	0.05 mg
			Per ml drops :	
			Metamizol	500 mg
			Pitofenone	0.5 mg
			Fenpiverinium bromide	0.1 mg

	BRAND NAME	MANUFACTURER	CONTENTS (continued)	
5.	SISTALGIN COMPOSITUM	Merck	Injection : per 5 ml ampoule	
			Pramiverine	2.25 mg
			Metamizol	2.5 g
			Tablet :	
			Pramiverine	2 mg
			Metamizol	250 mg
6.	VISCERALGINE FORTE	Organon	Tiemonium methylsulphate	25 mg
			Dipyrone	250 mg
			Codeine phosphate	10 mg
7.	BENZA FORTE	Takeda	Tripelennamine HCL	25 mg
			Metamizol	40 mg
			Phenacetin	50 mg
			Ethoxybenzamide	150 mg
			Codeine phosphate	5 mg
			Caffeine	50 mg
			Ephedrine HCL	5 mg
			Hesperidin methyl chalcone	15 mg
			Vitamin C	70 mg
8.	BONPYRIN	Takeda	Injection : per 2 ml ampoule	
			Metamizol	500 mg
			25% x 2 ml	
			50% x 2 ml	

	BRAND NAME	MANUFACTURER	CONTENTS (continued)	
			Tablet :	
			Metamizol	500 mg
9.	CONMEL	Winthrop	Dipyrone	324 mg
10.	DEPARON	Westmont	Dipyrone	300 mg
			Meprobamate	200 mg
11.	DOLO-ADAMON	Asta-Werke	Injection : per 2 ml ampoule	
			Ciclonium bromide	5 mg
			Noramidazophen	500 mg
			Tablet :	
			Ciclonium bromide	10 mg
			Noramidazophen	250 mg
			Codeine phosphate	14.4 mg
			Crotarbital	50 mg
12.	DOLO-NEUROBION	Merck	Injection : per 3 ml ampoule	
			Vitamins :	
			B1	100 mg
			B6	100 mg
			B12	1 mg
			Procaine	50 mg
			Dipyrone	500 mg

	BRAND NAME	MANUFACTURER	CONTENTS (continued)	
			Tablet :	
			Vitamins :	
			B1	50 mg
			B6	100 mg
			B12	100 mcg
			Dipyrone	250 mg
13.	METILON	Daiichi Seiyaku	Injection : per 2 ml ampoule	
			Sulpyrine (amount not given)	
14.	NOVALGIN	Hoechst	Injection : per 2 ml ampoule	
			Metamizol	500 mg
			Tablet :	
			Metamizol	500 mg
15.	SPASMOLYSIN	Pharmmalaysia	Atropine methonitrate	0.3 mg
			Papaverine HCL	15 mg
			Metamizole	500 mg
			Diazepam	2.5 mg

From the Table it can be seen that the manufacturers of both drugs are mostly foreign. Many of the countries where these companies are based have either withdrawn or banned Aminophenazone and Dipyrone preparations because of their toxicity. Others, like the Federal Republic of Germany (FRG), have restricted the use of Dipyrone for very severe conditions and banned its use in combination products. Yet the companies continue to manufacture their products and market them in Malaysia.

CHAPTER 7

DRUG INFORMATION IN MALAYSIA : AMINOPHENAZONE

(1) DIMS Information

There are two preparations of Aminophenazone listed in *DIMS Vol 14 No 3 October 1985*. Both are Group B Poisons. Both are used as antirheumatic, anti-inflammatory analgesics.

(2) Warnings and Contraindications : Inadequate Information

Under the notes on 'Antirheumatic, Anti-Inflammatory Analgesics', there is a section on 'Pyrazolones (eg Phenylbutazone and derivatives)'. Information on these drugs is given in the following manner :

'Contra-Indications : Blood dyscrasias, severe renal, cardiac or hepatic insufficiency; thyroid disease; gastrointestinal ulceration, patients in whom aspirin or other non-steroidal anti-inflammatory agents have induced an asthmatic attack, rhinitis, or urticaria. Hypersensitivity to pyrazolones.

Special Precautions : Should be reserved for use in treatment of rheumatic disorders where less toxic drugs have failed. Children under 14 years

and elderly patients. May cause fatal agranulocytosis. During prolonged therapy, frequent blood count is necessary. Sodium and fluid retention may occur. May reduce uptake of iodine by thyroid glands. Use with great caution, if at all, in persons receiving oral anticoagulants or hypoglycaemics as activity of the drugs is enhanced. May enhance the effects of phenytoin and sulphonamides. Persistent sore throat or fever must be investigated fully as it may signify bone-marrow depression. Do not administer concurrently with plasma protein bound drugs.' (DIMS October 1985: 120)

(3) Indications Given

The 'indications' listed for the drug are as follows :

AMIZONE (Weber)

'Indications : Acute exacerbations of rheumatoid arthritis and osteoarthrosis, ankylosing spondylitis.

C/I : Hypersensitivity to pyrazoles. Also see notes 3 section 4c.'

RHEUMOPYRINE (Ciech Polfa)

'Indications : Acute exacerbations of rheumatoid arthritis,

osteoarthrosis, ankylosing spondylitis.

C/I & S/P : See notes 3 section 4c.'

There is no specific warning against Aminophenazone-induced agranulocytosis, which can be fatal. Both the preparations of Aminophenazone also contain Phenylbutazone, another extremely potent drug which has been associated with blood disorders including aplastic anaemia, and a significant cause of deaths worldwide. It is banned or severely restricted in the UK, Norway, Federal Republic of Germany, Bangladesh, Japan, Italy, Sweden, Finland, USA, Australia and New Zealand.

CHAPTER 8

DRUG INFORMATION IN MALAYSIA : DIPYRONE

(1) DIMS Information

There are 13 preparations of Dipyrone listed in *DIMS Vol 14 No 3 October 1985*. All 13 are Group B Poisons. Dipyrone is used in 'analgesics and antipyretics', 'antispasmodics' and even 'cough and cold remedies'.

(2) Warnings and Contraindications : Inadequate Information

Seven of the Dipyrone preparations listed in *DIMS* are used as analgesics and antipyretics. Under the notes on 'Analgesics & Antipyretics' there is a section on 'Pyrazolones (eg aminopyrine, dipyrone, metamizol)'. Information on these drugs is given in the following manner :

'Special Precautions : May cause fatal agranulocytosis. Frequent white blood cell and differential counts are needed in prolonged therapy. Discontinue use at the first sign of blood count alteration.'

Instead of a bold warning and caution, information on agranulocytosis merely plays down the dangers of Dipyrone. Apart from this, the danger of Dipyrone-induced agranulocytosis is not

mentioned for each of the specific brand preparations of Dipyrone. Neither are the dangerous adverse reactions such as Stevens-Johnson Syndrome and anaphylactic shock anywhere included. Under Special Precautions (S/P) and contraindications (C/I), information is listed as follows :

* BONPYRIN (Takeda)
'S/P: See notes 5 section 4b.'

*CONMEL (Winthrop)
'C/I: Intolerance to antipyrine, aminopyrine, dipyrone. Liver disease. Concomitant use of chlorpromazine.
S/P: See notes 5 section 4b.'

*DEPARON (Westmont)
'C/I: Acute intermittent porphyria. Also see notes 5 section 4b.
S/P: Hepatic and renal dysfunction. Epileptic patients. Also see notes 5 section 4b.'

*DOLO-ADAMON (Asta-Werke)
'C/I: Narrow angle glaucoma, hypertrophy of the prostrate, mega-colon, granulocytopenia, acute intermittent porphyria, mechanical stenosis of gastro-intestinal tract, allergy to pyrazolone derivatives.
S/P: Reaction time may be affected; combination with alcohol.'

*DOLO-NEUROBION (Merck)
'C/I: Injection and tablet: Acute intermittent porphyria, pyrazolone allergy, congenital glucose-6-phosphate dehy-

drogenase deficiency, granulocytopenia. Caution in first trimester of pregnancy.

Injection : AV Block, bradycardia, cardiac decompensation.

S/P: See notes 5 section 4b.'

*METILON (Daiichi Seiyaku)

'C/I & S/P: See notes 5 section 4b.'

*NOVALGIN (Hoechst)

'S/P: See notes 5 section 4b.'

Five of the Dipyrone preparations listed in *DIMS* are used as antispasmodics. Under the notes on 'Antispasmodics', there is no mention of Dipyrone and warnings against agranulocytosis caused by the drug are not given. Under Special Precautions (S/P) and Contraindications (C/I), information is listed as follows :

*AVAFORTAN (Old Formula) (Asta-Werke)

'C/I: Megacolon, allergy to pyrazolones, acute intermittent porphyria. Also see notes section 1c.'

*BARALGIN (Hoechst)

'C/I & S/P: See notes section 1c and notes 5 section 4b.'

*SPASMOLYSIN (Pharmmalaysia)

'C/I: See notes section 1c and 1 section 4e.

S/P: See notes section 1c, 5 section 4b and 1 section 4e.'

*SISTALGIN COMPOSITUM (Merck)
'C/I & S/P: See notes section 1c and notes 5 section 4b.'

*VISCERALGINE FORTE (Organon)
'C/I & S/P: Glaucoma and prostatic carcinoma. Also see notes section 1c, notes 2 and 5 section 4b. Further see Organon Product Safeguards.'

One Dipyrone preparation listed in *DIMS* is used as a cough and cold remedy. Under the notes on 'Cough and Cold Remedies' there is no mention of Dipyrone or warning against agranulocytosis. The Contraindications for the preparation are listed as follows :

*BENZA FORTE (Takeda)
'C/I: Pyrine hypersensitivity. Also see notes section 3c.'

(3) Indications Given

All 13 preparations were recommended for trivial and general conditions like 'renal, gastric and intestinal colic, migraine, dysmenorrhoea (period pains), all colic conditions, post-operative pain, smooth muscle spasm, common colds, fever, headache, herpes zoster, acute pain and fever, sprains, tension and pains associated with common cold, influenza, shoulder-arm syndrome', and for their 'antipyretic, analgesic and antirheumatic effects'. These conditions are hardly 'serious' or 'life-threatening situations' which, according to *Martindale,* are the only situations where the use of the drug 'is justified' and 'where no alternative antipyretic is available or suitable'. The indications listed for each of the 13 preparations are as

follows :

*AVAFORTAN (Old Formula) (Asta-Werke)

'Indications: Colics of the biliary and urinary tracts, acute pancreatitis, angina pectoris, migraine, tenesmus, dysmenorrhoea and to facilitate parturition.'

*BARALGIN (Hoechst)

'Indications: Spasmolytic for all smooth muscle spasms, renal, gastric and intestinal colic, spasmodic dysmenorrhoea etc.'

*SISTALGIN COMPOSITUM (Merck)

'Indications: Painful spasms of smooth muscles in the following clinical situations : gastric and intestinal colic, dysmenorrhoea, biliary and renal colics and post-operative pain.'

*VISCERALGINE FORTE (Organon)

'Indications: Analgesic, antispasmodic and anti-inflammatory in conditions of renal colic, smooth muscle and gastro-intestinal spasms.'

*BENZA FORTE (Takeda)

'Indications: Common colds especially accompanied with cough and fever.'

*BONPYRIN (Takeda)

'Indications: Fever, headache, pain due to muscular and articular rheumatism, lumbago, sciatica, polyarthritis.'

*CONMEL (Winthrop)
'Indications: Acute pain and fever.'

*DEPARON (Westmont)
'Indications: Tension headache, neuralgia, sprains, tension, and pains associated with common cold, influenza, arthritis, bursitis, lumbago, sciatica and rheumatic fever.'

*DOLO-ADAMON (Asta-Werke)
'Indications: Intense pain such as severe spasmodic pain occurring in colics of bile duct and urinary passages, ulcer pains, dysmenorrhoea, post-operative and traumatic pain, neuralgia.'

*DOLO-NEUROBION (Merck)
'Indications: Neuritis and neuralgias, lumbago, cervical syndrome, shoulder-arm syndrome, ischialgia, skeletal-muscular disorders, herpes zoster.'

*METILON (Daiichi Seiyaku)
'Indications: Antipyretic, analgesic and antirheumatic effects.'

*NOVALGIN (Hoechst)
'Indications: Pain and fever.'

*SPASMOLYSIN (Pharmmalaysia)
'Indications: Various painful smooth muscle spasms such as intestinal, renal and biliary colic, pylorospasm and pain due to functional bowel disorders, pancreatitis.'

(4) Brands Indicating Dosages for Children

According to various research, many of the victims of Dipyrone-induced agranulocytosis and death were children.

Four brands of Dipyrone listed in *DIMS* indicated dosages for children. The four brands are :

*BARALGIN Tablet (500 mg); Dragee (250 mg); Per ml drops (500 mg) (Hoechst)
Dosage: Children: ½-1 tablet or 1-2 dragees three times daily
or 10-15 drops three to five times daily.
Infants : or 3-5-8 drops five to six times daily.

*CONMEL Tablet (324 mg) (Winthrop)
Dosage: Children: ½-1 tablet twice daily - three times daily
Maximum daily dose: 6-12 years - 2 g
Under 6 years - 1 g

*DEPARON Tablet (300 mg) (Westmont)
Dosage: Children: ½-1 tablet three times daily.

*NOVALGIN Injection (500 mg x 2 ml) (Hoechst)
Dosage: Children: 2-14 years: 0.5-2ml

It is noted that the various Dipyrone preparations listed in *DIMS* are recommended for such minor ailments as colds, fever and headache. Not only that, four brands are actually recommended for children as young as two years old, when records show that children form a large number of the victims of Dipyrone-induced agranulocytosis and death.

CHAPTER 9

ADVERTISEMENTS ON AMINOPHENAZONE AND DIPYRONE IN MALAYSIA

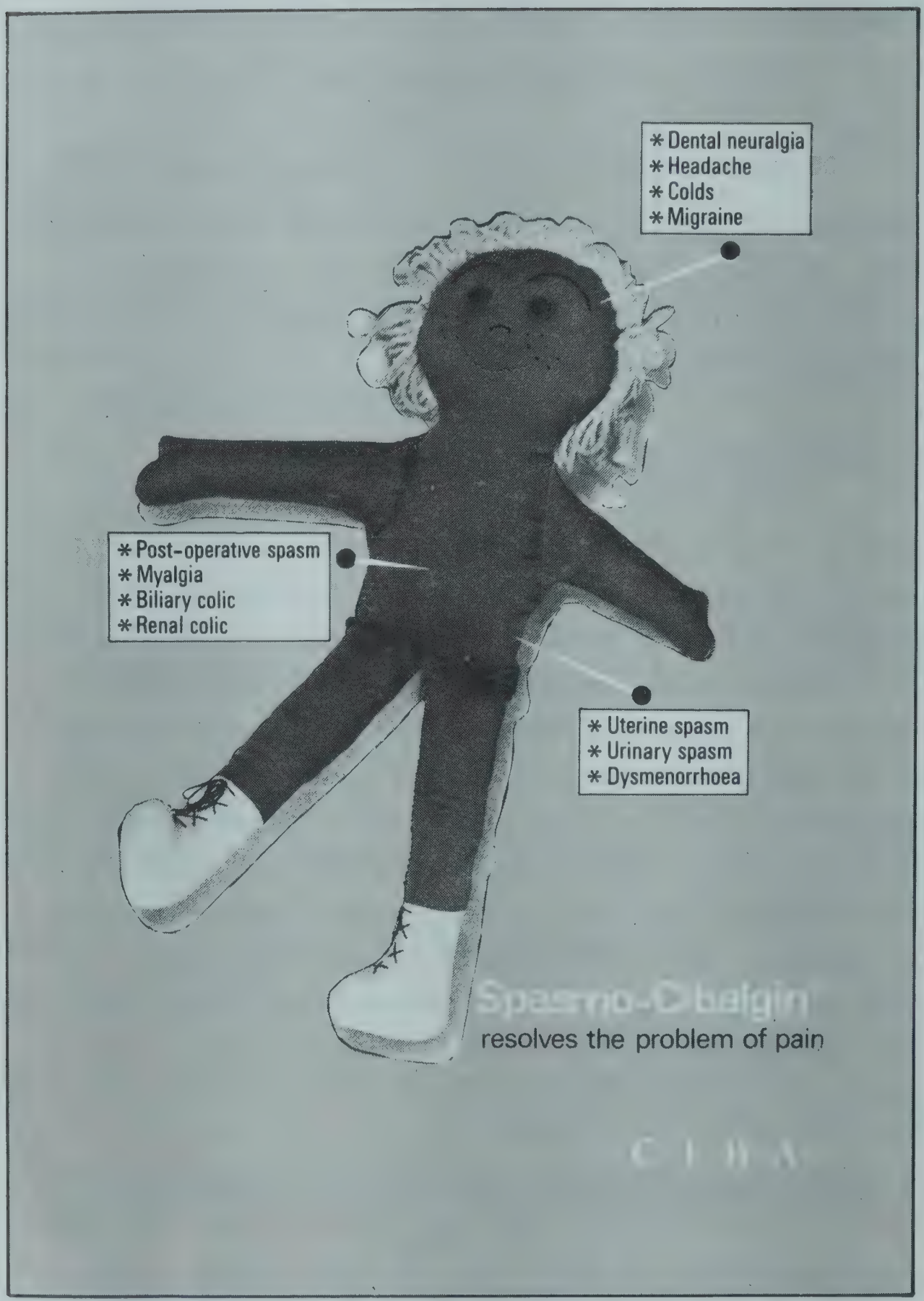
In this chapter, advertisements on both drugs which appear in *DIMS, The Family Practitioner,* brochures and promotional materials, as well as drug information inserts produced by the drug companies, are analysed.

(1) Advertisement on Aminophenazone in DIMS

In *DIMS Vol 7 No 1 1978* Ciba's SPASMO-CIBALGIN, which still contained Aminophenazone, despite having announced the re-formulation of all its Aminophenazone-containing products in 1977, continued to be marketed in Malaysia. SPASMO-CIBALGIN was advertised for a wide range of conditions from spasmodic pains to colds. There was an illustration of a rag-doll with arrows showing the conditions affecting the various parts of the body, for which the drug was indicated. These included dental neuralgia, headache, colds, migraine; post-operative spasm, myalgia, biliary and renal colic; uterine spasm, urinary spasm and dysmenorrhoea. There was no further information, nor warnings and precautions regarding the use of the drug.

(2) Advertisement on Dipyrone in *The Family Practitioner*

In the December 1983 issue of this quarterly journal (official journal of the College of General Practitioners of Malaysia),



Ciba's SPASMO-CIBALGIN, containing Aminophenazone, advertised in **DIMS** *Vol. 7 No. 1 1978.*

readers were advised to take the BARALGIN brand of Dipyrone 'when spasmodic pain' occurred. They were also urged to 'always rely on the proven and trusted answer', and Hoechst in the advertisement said that BARALGIN was the answer to 'immediate relief, reliable efficacy (and) pharmacologic action at all points of pain genesis'. The danger of Aminophenazone-induced agranulocytosis was not mentioned. In fact there was no further information provided apart from the catchwords quoted above.

In an advertising campaign in 1982, Hoechst had a BARALGIN quiz and lucky draw. Doctors were asked to answer some questions on BARALGIN on a form and prizes were offered for the first and second all-correct answers drawn. On the reverse side BARALGIN was advertised for 'quick action - fast relief' in conditions like 'colic, dysmenorrhoea, post-operative pain and management of labour pains'. It was stated that 'when spasmodic pain occurs ... Always rely on the proven and trusted answer BARALGIN'. The latter was repeated in the advertisement which appeared in *The Family Practitioner*.

(3) Drug Brochure for BARALGIN

In the drug brochure distributed to doctors BARALGIN is recommended for conditions ranging from renal and biliary colic to gastric and intestinal spasms, spasmodic dysmenorrhoea, anginal complaints, asthma and migraine. Under 'Indications and clinical results' Hoechst states that 'BARALGIN is highly effective in biliary and renal colic ... Also in other painful states of the biliary tract, meteric spasm and bladder tenesmus,

HOECHST's Lucky Draw

Rules

1. To enter the Lucky Draw, please tick the correct answer for the questionaires given on the next page.

2. Official entry forms are obtainable at the HOECHST's Hospitality Area. (Convention Hall Foyer)

3. Only completed entry forms will qualify for the draw.

4. Each entry form shall be valid only for the day's draw.

5. The draw will be held daily at the HOECHST Hospitality Area (Convention Hall Foyer) at 5.oo p.m. sharp.

6. The first prize will be given to the first all correct answer drawn. The second prize to the next correct answer drawn.

7. Prizes must be collected personally at the time of the draw.

8. The judges' decision is final.

Rules and entry form for the BARALGIN quiz and lucky draw, organised by Hoechst in 198

TEAR ALONG DOTTED LINE

HOECHST's Lucky Draw

Date: .....

Doctor's Name: .....
[*Please print*]

Address: .....

Speciality: .....

1. Baralgin is as effective as the mild narcotic analgesics (like pethidine) ☐ True ☐ False

2. Please tick the advantages related to Baralgin:

   ☐ Quick onset of action ☐ No sedation

   ☐ No addiction risk ☐ No respiratory depression

   ☐ Excellent antipyretic properties

   ☐ Oral and injectable presentations

3. Baralgin has no carcinogenic potential (ref: WHO Drug Information Oct-Dec 1979 No. PDT/DI/79.4) ☐ True ☐ False

4. Dipyrone is not among the list of drugs most frequently reported as associated with granulocytopenia, including agranulocytosis (ref: WHO Research Centre for International Monitoring of Adverse Reactions to Drugs).

   ☐ True ☐ False

.....
Signature

On the reverse side, Hoechst's advertisement on BARALGIN

Baralgin®

quick action – fast relief

Highly effective in spasmodic pain:

- Gastrointestinal colics
- Dysmenorrhoea

Highly effective even in severe conditions:

- Biliary colics
- Renal colics — equipotent to opiates
- Effective in post-operative pain
- Management of labour pains

Distinct advantages

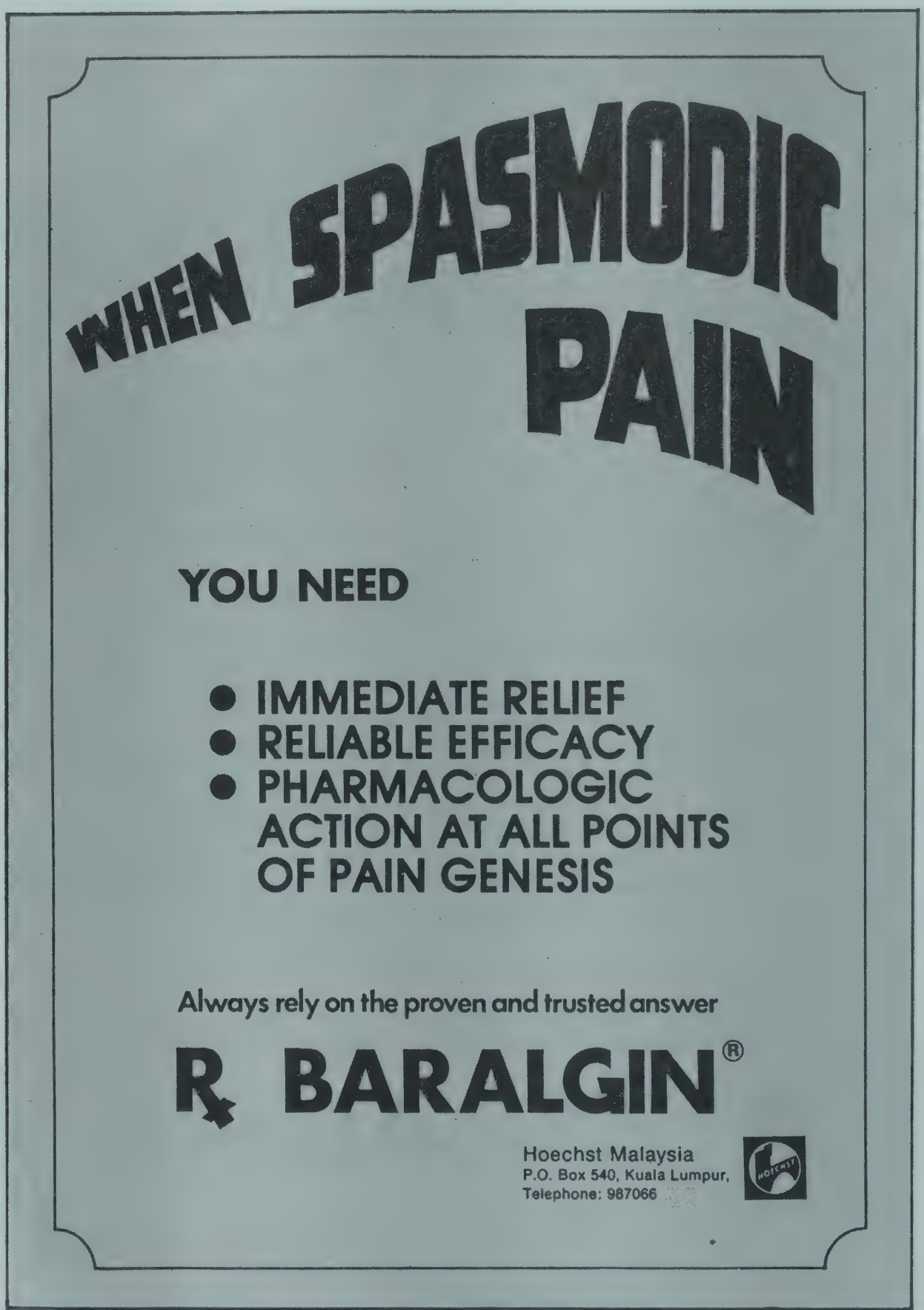
- Quick onset of action
- No sedation
- No addiction risk
- No respiratory depression
- Excellent antipyretic properties

Presentations available

- Tablet
- Dragee
- Injection
- Drops
- Syrup

Further information available on reqest.

Hoechst Malaysia
P.O. Box 540, Kuala Lumpur.
Telephone: 987066



Hoechst's advertisement on BARALGIN in **The Family Practitioner**, *Vol. 6 No. 3 December 1983. The same advertisement also appeared in* **Berita Farmasi**, *Vol. 6 1979.*

Information on BARALGIN, given in a brochure distributed to doctors

Indications and clinical results

Renal and biliary colic

BARALGIN is highly effective in biliary and renal colic. Slow intravenous injection of 5 ml. is recommended and is usually followed by **complete** relief of pain after a mean of 8 minutes, – in many instances even while the injection is still being administered. The effect is usually maintained over 5 hours. Also in **other painful states of the biliary tract, ureteric spasm** and **bladder tenesmus,** whether due to inflammation or mechanical irritation, BARALGIN is rapidly effective. During **expulsion of calculi** from the biliary and urinary tract intravenous administration together with administration of substances which stimulate peristalsis has been found effective.

BARALGIN may be used for **differential diagnosis,** for unlike colic induced by calculi peritoneal pain does not respond. Where X-ray findings are obscure owing to pronounced spasm examination under intravenous BARALGIN or control examination after a further intravenous injection often produce unequivocal results.

Gastric and intestinal spasms

BARALGIN therapy is effective in gastric and intestinal spasm of various aetiology, and also in abdominal pain after surgical procedures, due to tumours or adhesions.

Spasmodic dysmenorrhoea

In gynaecology and obstetrics BARALGIN is specially indicated in spasmodic dysmenorrhoea. Here the preparation not only has a symptomatic action but produces in many cases a lasting therapeutic effect. Also in lower abdominal pain during early pregnancy and in the treatment of **after-pains** the preparation has proved valuable.

In **retention of urine** post-partum and after abdominal operations micturition usually returns spontaneously within 20 minutes of administration of BARALGIN.

continued next page

Anginal complaints

In angina pectoris and myocardial infarction good results have been obtained; it should be stressed here that in contrast to morphine derivatives BARALGIN does not impair the oxygen supply to the heart.

Mild and moderately severe **attacks of asthma** can often be aborted by intravenous injection of 5 ml. BARALGIN.

In attacks of migraine, nocturnal shoulder / arm pain and diverse other states of pain associated with vascular spasm clinical experience indicates a trial with BARALGIN.

Application and Dosage

For injection, BARALGIN is available in ampoules of 2 ml. and 5 ml., and in a multidose container of 10 ml. In case of moderate spastic pain the intramuscular or slow (!) intravenous injection of 2 ml. may suffice.

In heavy pains, especially colics, the intravenous injection of 5 ml. BARALGIN is recommended (duration of injection: 2-3 minutes). The injection may be repeated, if necessary, after 6-8 hours.

For the treatment of slight and moderate pains, the application of suppositories, drops, tablets, or dragees is recommended. 1 dragee contains half of the active ingredient of 1 tablet.

Daily Dose	Tablets	Dragees	Drops	Supposit.	Supposit. for children
Adults	3 times 1-2	3-4 times 2-3	3-4 times 20-40	2-3 times 1	–
School children	3 times ½-1	3 times 1-2	3-5 times 10-15	1-2 times ½-1	–
Younger children	–	–	5-6 times 3-5-8	–	1-3 times 1
Infants	–	–		–	1-2 times 1

continued next page

Side-effects

All authors stress that BARALGIN is extremely well tolerated, regardless of the route by which it is administered. They emphasise that it does not induce habituation or addiction, nor does it make the patient feel tired so that it is of special value for ambulant therapy.

BARALGIN is well tolerated. However, in rare cases it may cause allergic reactions that necessitate discontinuation of the medication.

whether due to inflammation or mechanical irritation, BARALGIN is rapidly effective.'

It is even indicated for 'lower abdominal pain during early pregnancy and in the treatment of after-pains the preparation has proved valuable'.

Under 'Side-effects' Hoechst says that 'BARALGIN is extremely well tolerated, regardless of the route by which it is administered. However, in rare cases it may cause allergic reactions that necessitate discontinuation of the medication.' There is no single warning or mention of agranulocytosis, Stevens-Johnson Syndrome and anaphylactic shock in the brochure.

(4) Hoechst (Malaysia) Memo on Dipyrone

In a memo distributed to doctors in 1982 (see Appendix 1), Hoechst Malaysia Sdn Bhd described Dipyrone as a 'mild analgesic: being used since a very long time (1922) and extensively'. It went on to say that 'Considering that BARALGIN besides its very effective oral presentation is one of the most widely used and found to be very effective ... there is no doubt regarding its usefulness for the medical practitioner. The very rare occurrence of hypotensive episodes is no greater than that found with other I.V. (intravenous) injections.'

Hoechst also stated that 'Our company has since many years included comprehensive information for the physician and patient in the text of the packing and inserts of our relevant products.'

The memo gave a very inaccurate picture of Dipyrone, playing down the dangers of the drug. Not a single medical journal was quoted for the toxicity of the drug, and studies of adverse reaction to the drug documented worldwide were not referred to. Referring to the ban of Dipyrone in the USA, Hoechst in its memo said that 'This was on the basis of 13 cases of agranulocytosis observed over a period of 10 years. However the observation was not based on sound scientific methodology and was severely questioned in 1979 during the International Conference on Mild Analgesics.' This is contrary to the evidence documented between 1957-66 which revealed that 40 cases of agranulocytosis were linked to Dipyrone and a further 20 possibly due to the drug (see page 13).

Commenting on the Swedish ban, Hoechst attempted to convey that the side effects could be due to other drugs, not just Dipyrone alone. It vaguely mentioned Swedish researchers (no references given) who were alleged to have commented on government statistics that 'This could be taken as an indication that individual susceptibility plays an important role, more important perhaps than the offending drug. In other words, at least at a low degree of exposure to sensitizing drugs, a number of sensitive individuals will develop negative reactions to a variety of drugs.'

This only serves to heighten the dangers and unpredictability of the drug, since individuals can be sensitized to the drug even at a very low degree of exposure.

However, between 1966-70 the Swedish Adverse Drug Reaction Committee showed that agranulocytosis attributed to Dipyrone

had been reported on 27 occasions. It also noted that the reported figure represented one-third of the true frequency (see page 13).

Hoechst cited only four countries in which Dipyrone is banned, adding that reasons for its ban in these respective countries are unknown and no statistics are available. It concluded that: 'In all other parts of the world, Pyrazolones including Dipyrone are available after its launch in 1922 with the exception of UK and Canada where it was never introduced.'

This is misleading because more than four countries have banned Dipyrone (see Chapter 4). Hoechst is therefore giving the false impression that almost all countries permit the use of the drug. Hoechst Malaysia therefore implies that it must be a very popular drug and that it cannot be all that dangerous. Hence Malaysian doctors need not fear using Dipyrone.

Hoechst Malaysia is in fact giving a one-sided view to promote the use of its Dipyrone preparation to local doctors. The distortion of facts and misinformation presented in the memo is highly unethical and irresponsible.

Generally, advertisements in Malaysia for the two drugs are quite misleading, in that they do not give a true picture of the dangers of the drugs. Instead, the advertisements frequently make the drugs appear to be wonderful cure-alls, promising effective relief from ailments ranging from colds to spasmodic pains.

CHAPTER 10

DRUG INFORMATION INSERTS IN MALAYSIA : DIPYRONE

Drug inserts, that is, information concerning the use, dangers and precautions to be taken for the drug, which come together with the product, were also examined.

There have been enough warnings about the dangers of Dipyrone. According to *Meyler's Side Effects of Drugs, 90th Edition,* for example, 'there can be no doubt that Aminopyrine and Dipyrone cause agranulocytosis ... Since effective, less dangerous alternative drugs are available there is no case for the continued use of Aminopyrine and Dipyrone' (Meyler's 1980: 63-4).

The *AMA Drug Evaluations* also points out that the only justifiable use of Dipyrone 'is as a last resort to reduce fever when safer measures have failed .... Because Dipyrone may produce fatal agranulocytosis and other blood dyscrasias, its use as a general analgesic, antiarthritic, or routine antipyretic cannot be condoned' (AMA Drug Evaluations 1973: 262, 267).

Yet, the drug inserts found in Malaysia recommended the drugs for a wide variety of ailments and many of the dangers of the drugs were not sufficiently stressed.

(1) Drug Information Insert for BONPYRIN (See Appendix 2)

In the drug insert, manufacturer Takeda describes BONPYRIN as an 'Antipyretic and Analgesic', and a 'brand of sulpyrin J.P. ... one of the most effective preparations among antipyrine derivatives for fever and pains'. It is indicated for 'headache, pain of muscular and articular rheumatism, lumbago, sciatica, polyarthritis, myositis, influenza and other febrile condition'.

No contraindications are listed.

Under 'Caution' is mentioned 'Sulpyrin may cause agranulocytosis' and 'Store away from light'.

This plays down the real danger of BONPYRIN-induced agranulocytosis. Moreover, using 'Sulpyrin' to describe Dipyrone or Metamizol - the more common generic names - can confuse or mislead the doctor into thinking that this drug is dissimilar. No mention is made that Dipyrone can cause fatal anaphylactic shock, severe lesions and Stevens-Johnson syndrome.

(2) Drug Information Insert for BARALGIN (See Appendix 3)

In the drug insert, manufacturer Hoechst says BARALGIN is 'particularly suitable for the relief of painful smooth muscle spasms ...'.

It is indicated for 'renal colics, ureteral spasms, vesical

tenesmus (ineffectual and painful straining in urination), biliary colics and dyskinesias (impairment of voluntary movement), gastrointestinal spasms. Spastic dysmenorrhoea. Migrainous headache'.

All the information is written in very small print. Hoechst also recommends BARALGIN in a paediatric preparation for infants only four months old.

Under 'Side effects' is stated that 'BARALGIN may occasionally produce hypersensitivity reactions in the form of skin changes or reduced blood leukocyte count or, in very rare cases, agranulocytosis'. This important information should be given under 'Warning' or 'Precaution'. By inserting it under 'Side effects' Hoechst is downplaying the real dangers of the drug and its toxicity.

Interestingly, at the bottom of the insert, in fine red print Hoechst states in Bahasa Malaysia: *'Amaran: Ubat ini mungkin mengakibatkan agranulocytosis yang membawa maut.'* Translated, it means: 'Warning: This drug may cause agranulocytosis which can bring death.' As the information and instructions in the insert are written in English, this incongruity serves to play down the dangers as in all likelihood, the doctors will not bother to pay notice to the warning in Bahasa Malaysia.

Under 'Please Note' is written: 'Without the doctor's instructions this preparation should not be taken in high doses or for prolonged periods of time.' This could imply that BARALGIN can be dispensed by persons other than doctors and can be

taken by a patient without a 'doctor's instructions' so long as the dosage table on the insert is adhered to. Hence self-medication is encouraged.

(3) Drug Information Insert for BENZA FORTE (See Appendix 4)

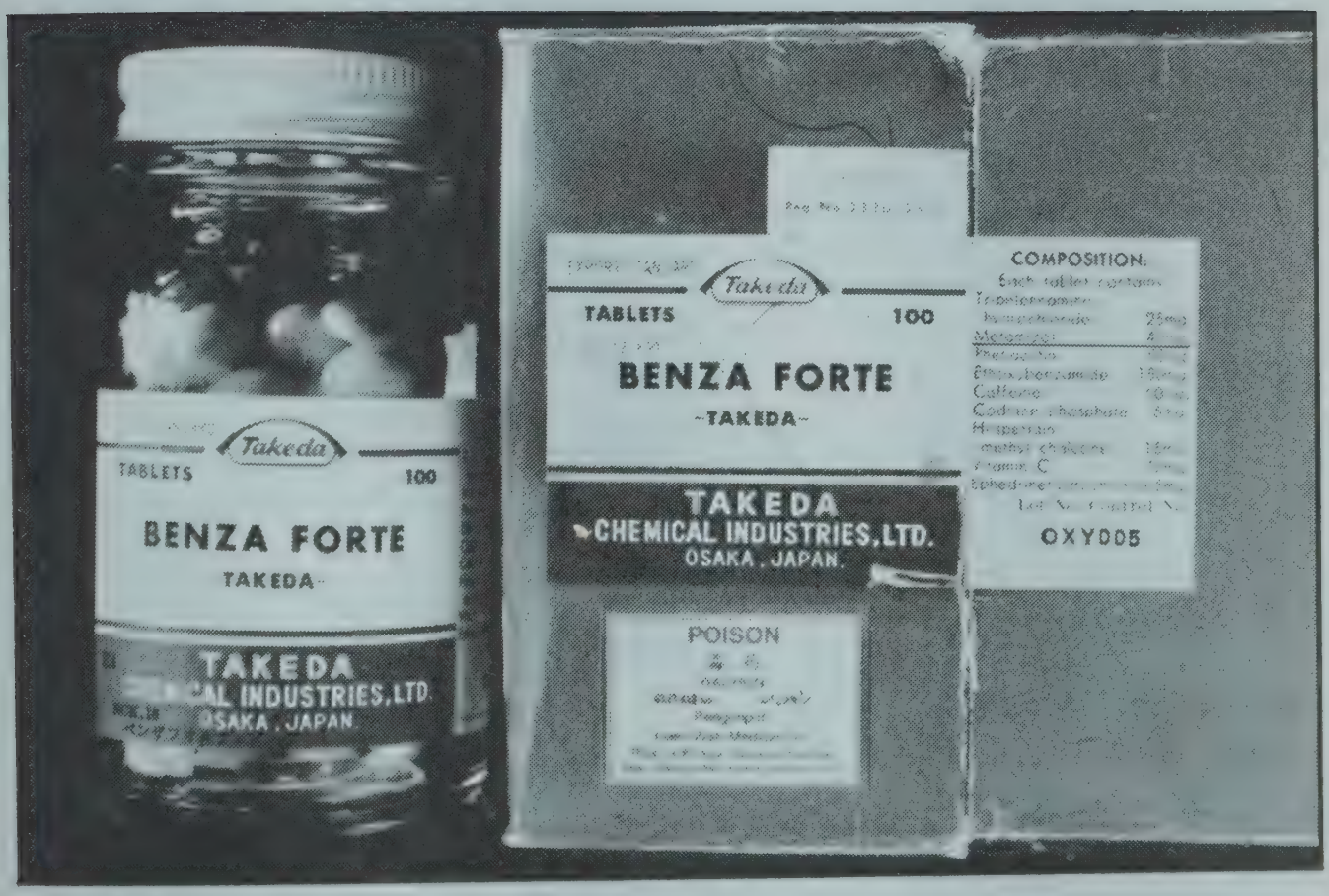
In the information insert for BENZA FORTE, manufacturer Takeda describes it as 'a cold tablet ... It possesses a marked effect in the treatment of various types of colds'. It is indicated for 'common colds (especially accompanied by cough and fever), coryza, influenza, headache, toothache, pain following dental surgery'.

BENZA FORTE contains nine ingredients including Vitamin C, caffeine and Phenacetin. Phenacetin has been withdrawn from use in at least 12 countries because it can lead to kidney and liver damage with prolonged use. Combined use of caffeine and Phenacetin can give rise to addiction as well.

No Contraindications are listed. Under 'Precautions' is stated that :

1) Drowsiness may occur in sensitive patients.
2) Caution is required in individuals sensitive to antipyrine derivatives.
3) Should not be used for infants below six years old.

Under 'Administration and Dosage', 'one tablet, three times daily' is recommended.



BENZA FORTE tablets, a cold remedy containing Dipyrone

No mention is made of the dangers of Metamizol agranulocytosis. The information in the insert plays down the dangers of both Metamizol and Phenacetin.

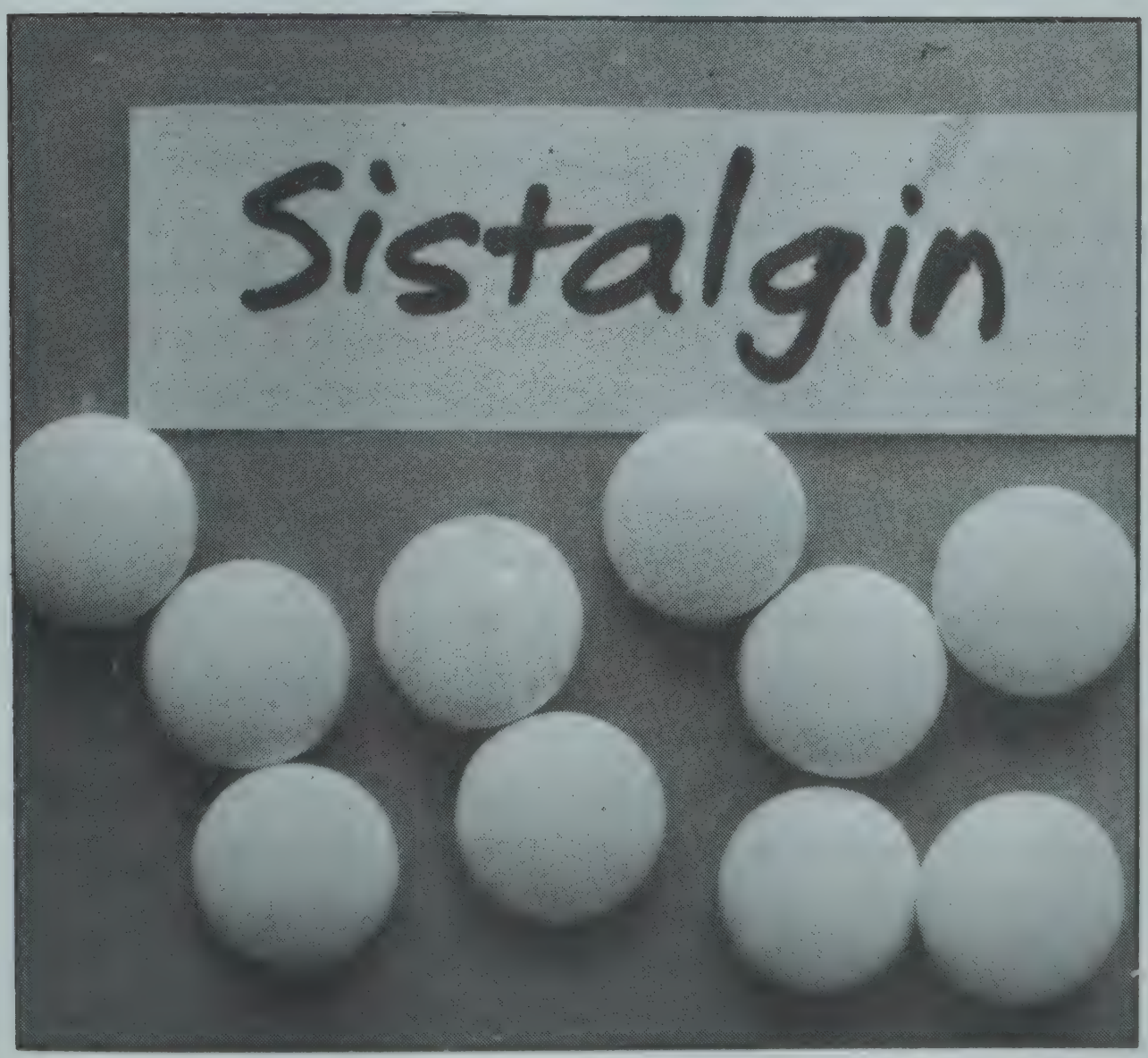
Japan removed the Dipyrone ingredient from all proprietary cold medicines and antipyretic-analgesics in 1977. In 1984, Takeda in Japan informed its Southeast Asian subsidiaries to stop the sale of its Dipyrone cold remedy BENZA D. Yet in Malaysia, BENZA FORTE, a cold remedy containing Dipyrone, continues to be marketed. This is clearly an instance of double standards in marketing and dumping.

(4) Drug Information Insert for SISTALGIN COMPOSITUM (Comp) (See Appendix 5)

In the insert the drug is indicated for 'painful spasm and colic in ... Gastro-intestinal tract (eg peptic ulcer), Biliary tract, Urinary tract (eg irritable bladder), Gynaecological disorders (like menstrual pain), and post-operative pain ... a wide variety of surgical procedures'.

Under 'Side effects' manufacturer Merck says 'Cases of agranulocytosis have been reported following the use of metamizol in certain predisposed patients.' In this way, the dangers of agranulocytosis are played down.

Under 'Dosage' Merck says 'Dosage with SISTALGIN COMP depends on the intensity of the pain.' It recommends '1 tablet (250 mg) 3 times daily. On the first day up to 2 tablets three times daily may be given if required.' This amounts to 1500 mg. In 'acute



SISTALGIN COMPOSITUM tablets, which also contain Dipyrone

cases, single dose of 1 to 2 ampoules (1 ampoule = 2500 mg) by slow i.v. or i.m. injection is recommended.' This single dose may be equivalent to 2500-5000 mg of Dipyrone. It goes on to say that 'the daily dose should not exceed four ampoules (10000 mg)'.

(5) Drug Information Insert for NOVALGIN (See Appendix 6)

In the insert, manufacturer Hoechst describes the drug as a 'highly effective analgesic, spasmolytic, antirheumatic and antipyretic'. It is indicated for 'various kinds of pain, such as headache, neuralgia, sciatica, lumbago, etc - Biliary and renal colics (in these cases NOVALGIN injection is often substituted for the usual alkaloids) - Muscular rheumatism and polyarthritis (preferably large parenteral doses ie administered intravenously or intramuscularly) - Influenza and frebrile diseases'.

The insert does not give the generic name of NOVALGIN. It only lists the quantity of the drug in the Tablets, Drops, Suppositories and Injections. This is most unethical and misleading as any doctor may be persuaded to believe that NOVALGIN is both effective and safe.

This is made worse by the fact that there are no Contraindications, Warnings or Precautions listed in the insert. Under 'Tolerability' Hoechst says 'Novalgin is well tolerated. However in rare cases it may cause allergic reactions that necessitate discontinuation of the medication.' It further adds that 'Analgesics should not be taken in high doses or over prolonged

periods without consulting the physician.' This information implies that it is all right to take NOVALGIN on your own, thus encouraging self-medication. Again, nowhere is it mentioned that NOVALGIN can cause agranulocytosis.

Hoechst specifically markets NOVALGIN for infants in drops. Under 'Dosage' the company says 'Novalgin in the form of drops has proved to be particularly useful in paediatrics.' The drops are recommended for use in 'children from 4 months to 5 years'. The tablets are recommended '3-4 times daily' in quantities of 1-2 tablets. This is equivalent to 1500-2000 mg and 3000-4000 mg daily (1 tablet = 500 mg).

(6) Drug Information Insert for DOLO-NEUROBION (See Appendix 7)

In the drug information insert for DOLO-NEUROBION (Neurotropic Vitamins and Analgesic), Merck states that 'metamizol is of particular advantage especially in the presence of severe pain where rapid relief is desired. Therefore, Dolo-Neurobion coated tablets are prescribed in all painful conditions of the nervous system and the spine'.

Under 'Note' it says that 'DOLO-NEUROBION is well tolerated. In rare cases, however, a sensitization due to metamizol may occur and require discontinuation of therapy.'

On top of the drug information insert, stamped in small print, is 'Warning: This drug may cause fatal agranulocytosis.'

Under 'Dosage' is stated 'Unless otherwise prescribed by the physician, 3 times daily 1-2 coated tablets.' This implies that anyone can prescribe for oneself 750 mg to 1500 mg of the drug daily without a doctor's supervision. Again it would appear that self-medication is encouraged. Administration of the drug is left entirely to the individual.

(7) Drug Information Insert for DOLO-ADAMON (See Appendix 8)

In the drug insert for DOLO-ADAMON, Asta-Werke uses the chemical name Pyrazolonemethylaminomethane sulphonate (Noramidazophen) instead of Dipyrone or the other more common generic names.

The drug is recommended for 'quick and reliable relief from severe painful conditions' with 'long lasting effects'. It is indicated for 'all severe painful conditions (e.g. colics of the biliary ducts, the urinary passages, bladder tenesm (pain during urination), ulcer pain, dysmenorrhoea; postoperative and post-traumatic pain, neuralgia (e.g. sciatica, slipped disc), migraine, pain occurring within the ear, nose and throat region, myalgia (pain in the muscles), tumour pain, parturition (labour pains) (i.v.) etc.'

Under 'Side effects' is stated that 'In very sensitive patients, Dolo-Adamon may lead to allergic skin reactions, very rarely to granulocytopenia.' This plays down the side effects of the drug. Nowhere is it mentioned that this drug may cause fatal agranulocytosis.

Under 'Dosage' it reads 'If not otherwise prescribed by the physician, Coated tablets: 1-2 tablets two or three times daily.' This means that the user is encouraged to take 500-1500 mg of the drug daily.

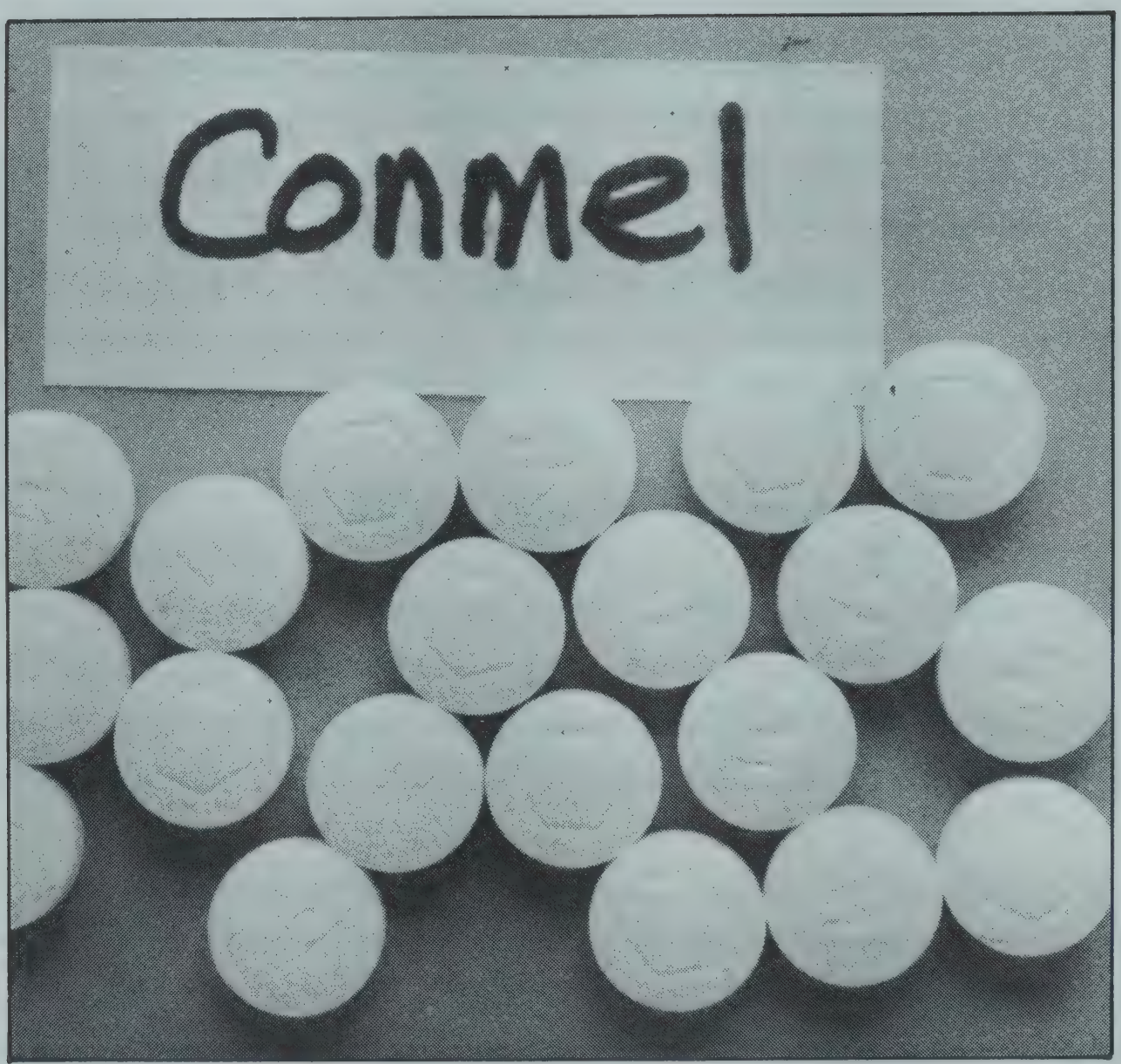
From the information provided, it can be seen that the dangers of the drug are deliberately played down. The use of the uncommon name for the drug may lead doctors to think that it is not related to Dipyrone and its notorious sister drug, Amidopyrine. There are no warnings listed against its use. In fact it is recommended for a number of conditions ranging from menstrual pains to migraine and labour pains. Most important, the possibility of fatal agranulocytosis with the use of the drug is not mentioned at all.

(8) Drug Labelling for CONMEL (See Appendix 9)

CONMEL, which contains 324 mg of Dipyrone, is sold in hospital packs containing 1,000 tablets. There are no drug inserts as the drug is marketed in bulk quantities. The only information about the drug is listed on the label of the pack when it is purchased.

Under 'Indications' on the pack label, the preparation is recommended for 'headache, neuralgia, rheumatism, lumbago, biliary and renal colic, and pain due to colds, influenza and other infectious diseases'.

There is a 'Warning' which states that 'This drug may cause Fatal Agranulocytosis.'



CONMEL tablets, which contain Dipyrone

Under 'Dosage', CONMEL is recommended for 'Adults - One or two tablets, three or four times daily. Larger doses may be given when required, particularly in arthritis, under medical supervision.' This works out to 972 or 1296 mg, to 1944 or 2592 mg daily.

One can see that the doses recommended are extremely high with a range from 972 mg to 2592 mg, which is more than double in quantity.

Although it is mentioned that a heavier dose is recommended under medical supervision, this implies that the drug can also be administered by anyone dispensing the drug, if the dosage does not exceed the 972-2592 mg range.

This kind of instructions for taking the drug can only be considered highly irresponsible (apart from the fact that the drug is recommended for trivial complaints like headache and influenza); and the warning against agranulocytosis does not in any way mitigate the unethical intentions of the drug company in promoting its drug.

In fact, apart from the warning, there are no precautions listed or any further instructions to warn against adverse drug reactions and their symptoms.

The absence of sufficient and necessary information and warnings by the company is most disturbing considering the extreme toxicity of the drug.

(9) Drug Labelling for BUSCOLYSIN COMPOSITUM (See Appendix 10)

BUSCOLYSIN COMPOSITUM, which contains Dipyrone (250 mg), is sold in hospital tin packs containing 1,000 dragees. No drug inserts are given. The only information about the drug is listed on the label of the pack when it is purchased.

Under 'Indications' on the pack label, the preparation is recommended for 'Acute spastic spasms of the gastrointestinal tract. Biliary colic, renal colic and other conditions of paroxysmal abdominal pain. Painful spastic conditions of the female genital system; dysmenorrhoea (menstrual pain)'.

Under 'Contraindications' the label reads that 'Children under 12 months of age should not be given BUSCOLYSIN COMPOSITUM .... prolonged administration is inadvisable, particularly in patients with a history of drug allergy or blood dyscrasia.'

The dangers of the drug are played down. There is no warning of Dipyrone-induced agranulocytosis and side effects of the drugs are not listed. In fact the drug is recommended for children above 12 months of age, and the tablets are sugar coated.

Under 'Administration and dosage', instructions list '1-2 tablets, if necessary 3 times a day until pain is relieved'. This would mean a daily dose of 1500 mg. There is no special dosage or instructions for use listed for children on the label and it would appear that the administration of the drug to children is left entirely to the discretion of the doctor or anyone else dispensing the drug. In the absence of sufficient and necessary information

given by the company, this is most disturbing considering the extreme toxicity of the drug.

From the examples given above, it can be seen that Dipyrone and its related drugs have been promoted for complaints which are hardly life-threatening, such as headache, influenza, labour pains and migraine. This is in spite of the very severe warning that 'The use of Dipyrone is justified only in serious or life-threatening situations where no alternative antipyretic is available or suitable' (Martindale 1982:251).

The dangers of the drug are deliberately played down; and the dangerous side effects such as agranulocytosis, Stevens-Johnson Syndrome and anaphylactic shock are either excluded from the warnings and precautions or casually mentioned.

It must also be realized that many of the brands can be bought over the counter in pharmacies and drug stores. This is especially true of those brands which are marketed in bulk to pharmacists, who then sell loose quantities of the drugs to consumers.

These drugs are not only powerful painkillers but in the wrong hands they can be lethal. Recommending them for the most trivial of ailments like fever, coughs and colds and stomachache is most reprehensible. The Ministry of Health must act at once to ban the sale and use of this drug and its other chemical derivatives, in line with the action taken by other countries, for the health and safety of all consumers.

CHAPTER 11

CASE REPORTS OF TOXICITY

By the 1970s, when the dangers of fatal agranulocytosis linked to Aminophenazone use became increasingly clear, many countries began to either ban or impose severe restrictions on the use of the drug. In 1977 Switzerland withdrew the drug, and the Swiss companies Ciba-Geigy and Sandoz announced that their pain and fever remedies containing Aminopyrine would be removed from the market or reformulated by the end of that year. Hoechst also announced it would take similar steps. (Silverman, Lee and Lydecker 1982:61). However the reality was far removed from the truth in the Third World.

(1) Aminopyrine-induced Agranulocytosis in Mozambique

Below is an account of how Aminopyrine had been used in Mozambique a Third World country, in 1979 and the tragic consequences that en for the victim, who suffered from Aminopyrine-induced agranulocytosis. This case has received worldwide attention in both medical journals and the press. It has been used as a classic example of double-talk and double standards practised by the drug multinationals, in this particular case Ciba-Geigy, in the Third World. Information on the case history is taken from *New Scientist, Lance* and *New Statesman*.

In August 1979, a 27-year-old English school-teacher Carol Gates working in Beira, Mozambique, East Africa, developed a slight fever along with a sore throat and aches in her arms, legs and back. She bought a packet of 20 tablets called CIBALGIN made by the Swiss company Ciba-Geigy without prescription from a local pharmacy, and started taking them according to the instructions.

After four days, however, the fever had become worse. Painful white spots appeared in her mouth and on her gums. Ulcers were forming on her lips, and there was tooth pain, colicky pain in her abdomen, and vomiting.

Two weeks later, her face was swollen beyond recognition and her gums were turning black. She was running a temperature of over 40°C (105°F). Infections developed along the veins of her arms and she was too weak to stand.

Two days later, she was admitted to the hospital in Mozambique after a test showed that her white blood cell count had dropped to a dangerous level (it was one-fifth of the normal level). The doctors tried to control what seemed to be some baffling infection. In spite of the treatment, more ulcers broke out on her palate and lower lip, and red streaks and nodules appeared on her limbs and body.

Still suffering from the fever, the ulcers, and a necrosis (death of part of a living body) which eventually exposed both her upper and lower jawbones, she was flown to the Reitfontein Hospital in Johannesburg, in a critical condition.

Her condition further deteriorated and the infection which had begun in her mouth erupted all over her body. She developed lung abscess, too. The flesh of her lips and gums fell away, diseased. So was a part of her exposed jawbone.

The team of doctors from the National Institute of Virology, whose care she was under, ran a battery of tests but could not find any virus implicated in her condition. They succeeded only in diagnosing the unusual bacteria responsible for the secondary infections. Having eliminated the viral cause for the dramatic reduction in her white blood cell count, the team next asked what drugs she had taken, and she mentioned CIBALGIN. There was no need to look any further. Finally, after six weeks of hospital treatment, the acute state was brought under control.

Carol Gates survived the trauma but some part of her gums disappeared and she would need surgery to remove the dead bone in her mouth.

She had suffered from agranulocytosis as a result of Amidopyrine. It was this sharp fall in the production of white blood cells in her body that made her vulnerable to potentially fatal secondary infections.

Carol Gates' case was further highlighted and raised by two doctors - Dr Paul Epstein, who treated her, and Dr John S. Yudkin, formerly of the Faculty of Medicine, Dar-es-Salaam, Tanzania - in a letter to the *Lancet* on 2 August 1980.

In a personal communication with Dr Milton Silverman in 1981,

Dr John Yudkin said of Carol Gates that 'she came very close to dying. Her weight had dropped from 110 lbs to 70 lbs. She had to be given substantial oral surgery and dental care. But she survived. If she had been some poor Mozambican peasant woman, she would not have had the investigations that made it possible to diagnose her condition. It's possible that many people throughout the Third World die every day from drug-induced illness that is put down as malaria or some other disease' (Silverman, Lee and Lydecker 1982:62). In fact, the package of CIBALGIN that Gates bought was labelled for sale in countries such as Nicaragua, El Salvador and the Netherlands Antilles.

In 1977 Dr Yudkin, then in Tanzania, had found on the market nine Aminopyrine products manufactured by Asta, Hoechst, Boehringer-Ingelheim, Ciba-Geigy and Sandoz. He calculated that the amount of such drugs used in Tanzania in 1976 would very likely have killed 630 people in that year.

According to the *New Scientist* correspondent writing from Mozambique, only two weeks after Carol Gates had been evacuated from Mozambique, a Ciba-Geigy salesman arrived in the Central Hospital in Maputo, the capital, to distribute free samples of CIBALGIN. This was despite a letter that Ciba-Geigy (and Sandoz) had sent two years earlier (in February 1977) to doctors, announcing their intention to reformulate all products containing Amidopyrine before the end of the year.

According to the *New Statesman* report in August 1980, 'The Monthly Index of Medical Specialities (MIMS) Africa, for March 1980, the latest available, includes products containing Amidopyrine from

Ciba-Geigy, Sandoz, Hoechst, Ranvensburg (West Germany) and Polfa (Poland). It would be impossible to estimate how many Africans have taken the drug and suffered side effects similar to those which afflicted Carol Gates.'

That CIBALGIN was available in Africa in 1980 when it was already withdrawn from its country of origin, Switzerland, in 1977 is no isolated incident. In the summer of 1980 Carol Gates herself discovered Ciba-Geigy's CIBALGIN containing the original Aminopyrine formulation stocked in a modern pharmacy in Portugal (Silverman, Lee and Lydecker 1982:62).

And in January 1980, CAP staff purchased the original CIBALGIN over the counter in a pharmacy.

In calling upon the WHO to control the marketing practices used by the pharmaceutical industry in the Third World, Drs Epstein and Yudkin in their letter to the *Lancet* wrote, 'Pharmaceutical companies act as a hazard to health when they fail to apply to exports to the Third World the same criteria from marketing and promotion that are adopted in industrialized countries' (Lancet 1980,2:254).

Ciba-Geigy's marketing of the drug conforms to the letter of the law of Mozambique. Similarly, elsewhere in the Third World, Ciba-Geigy's explanation would be that 'no country had enacted a law requiring the company to go through each pharmacy and remove CIBALGIN from its shelves' (Silverman, Lee and Lydecker 1982:62).

Carol Gates after her recovery from her near-fatal illness induced by CIBALGIN

®Cibalgin

Analgesic and antipyretic

Composition	0.03 g. diallylbarbituric acid + 0.22 g. aminophenazone per tablet and per suppository for children; 0.06 g. diallylbarbituric acid + 0.44 g. aminophenazone per suppository for adults and per ampoule of 2 ml.
Properties	Cibalgin, which exerts both central and peripheral effects, relieves pain and induces sedation; it also has an antipyretic action.
Indications	Painful conditions of all kinds, e.g. headache, toothache, neuralgia, post-operative pain, traumatic pain, dysmenorrhoea, etc.; insomnia due to pain; feverish colds, chills, and influenza.
Dosage	Adults: 1–2 tablets once or twice daily or 1 suppository of 0.5 g. 1–3 times daily; if necessary, 1 ampoule may be injected intragluteally or slowly i.v.—but not subcutaneously—up to 3 times daily. Care should be taken to avoid deposition of the drug in the region of a nerve. Infants: ½ suppository of 0.25 g. once or twice daily. Small children: ½ tablet or 1 suppository of 0.25 g. once or twice daily. Children of school age: 1 tablet or 1 suppository of 0.25 g. 1–3 times daily.
Note	Cibalgin should not be used in patients who are hypersensitive to pyrazolone derivatives. Prolonged, uninterrupted treatment with Cibalgin should, as a rule, be avoided; in cases where the drug is nevertheless taken on a long-term basis, it is advisable to carry out a blood count periodically (to detect possible signs of leucopenia).
Packages	12, 25, 100, and 1,000 tablets; 5 and 50 suppositories for adults; 5 and 50 suppositories for children; 5 and 100 ampoules.

Drug information on CIBALGIN, provided to members of the medical profession by the manufacturer in Malaysia.

The original CIBALGIN preparation, containing Aminophenazone, which CAP staff bought from a pharmacy in Butterworth in 1980.

(2) Aminophenazone- and Dipyrone-induced Adverse Reactions in Malaysia

Although Malaysia does not have data on case studies of side effects of Aminopyrine and Dipyrone, CAP in a personal interview with a pharmacologist attached to the University Hospital in Kuala Lumpur was informed that these two drugs were among the five which accounted for the majority of the adverse drug reactions suffered by patients admitted to the hospital. CAP was also informed by another specialist of one case of Dipyrone-induced adverse reaction which occurred in October 1980 at the General Hospital, Kuala Lumpur.

According to the specialist, a 48-year-old female was given an injection of the BARALGIN brand of Dipyrone by a GP for abdominal pain. She developed severe purpuric rash (small haemorrhagic spots in the skin) and had to be admitted to the hospital.

(3) Dipyrone-induced Adverse Reactions in Children

Doctors in hospitals and clinics in Malaysia have reported many cases of poisoning and even deaths, especially among children, due to the BONPYRIN brand of Dipyrone. One paediatrician CAP interviewed said that 'BONPYRIN should be banned from the face of this earth. I have seen two children die of anaphylactic shock (severe allergic reaction) after having been administered with the drug.' According to him, one reason why the drug is widely used by doctors is that it is very cheap. According to the price listed in DIMS, one BONPYRIN tablet costs only 7.3 cents (US3.7 cents) and a 25% X 2 ml ampoule for injection

is 38 cents (US19 cents).

Below we give three cases of BONPYRIN poisoning told to CAP by the same paediatrician interviewed above.

Case I

'This happened in 1976 to a four-year-old child. She had a cough and a cold and was running a fever for about four or five days. The frantic parents took her to see one GP after another, but her high fever did not subside. Finally one doctor gave her a shot of BONPYRIN. Within the hour, the child turned blue and stopped breathing. By the time she was brought to the hospital, she was already dead because of hypersensitivity to the drug causing a lowered blood pressure and shock.'

Case II

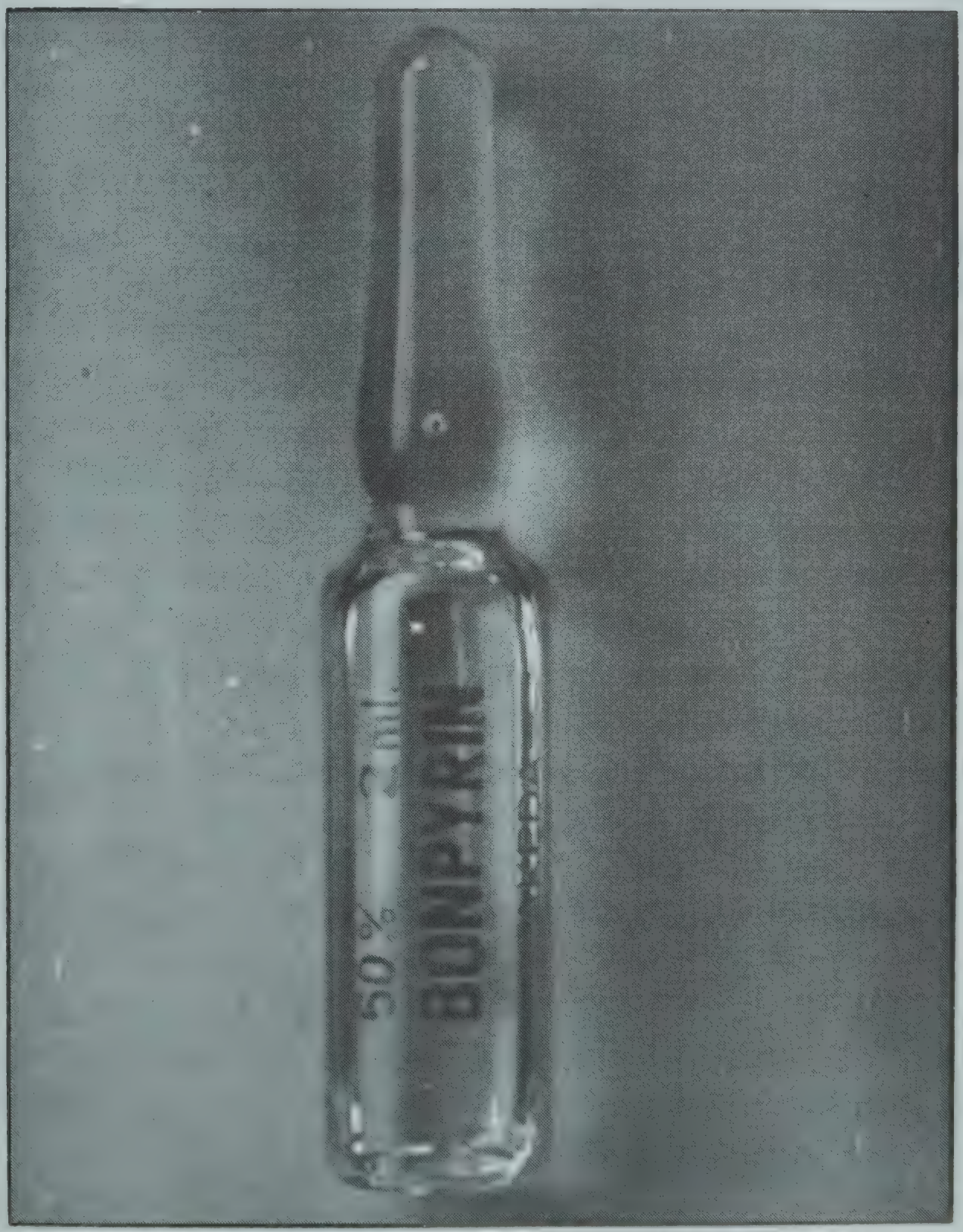
'Another child was also a girl about the same age. She was brought in very breathless. Her B.P. (blood pressure) was not recordable soon after an injection of BONPYRIN - about half an hour previous to this. We did all we could to resuscitate her. But she never recovered.'

Case III

'This was a case of a nine-year-old boy which took place in October 1980. He had fever for five days running and also had a cough and a cold. The mother took him to see a GP who was also a relative. The doctor gave the boy various types of medicine

and an injection of BONPYRIN. His condition did not improve. On the third day, the boy complained of chest pain and collapsed. He broke into a heavy sweat. When he was brought to the hospital he was unconscious. His blood pressure was unrecordable and the pulse was thready and feeble. His vomitus was dark in colour. We rushed him to intensive care and started resuscitating him. We managed to revive him. If he had come 15 minutes later he would have died. It was touch and go.'

The case studies mentioned clearly illustrate the double standards in marketing and promotion practised by the pharmaceutical multinational corporations in the Third World, and the terrible, often fatal, effects of Aminophenazone and Dipyrone. The Malaysian cases also prove how imperative it is for greater control to be exercised over the two drugs. A total ban on the drugs seems to be the only logical solution to the problem.



A BONPYRIN ampoule. The preparation has caused the death of so many children that a paediatrician has declared, 'BONPYRIN should be banned from the face of this earth.'

CHAPTER 12

OVERPRESCRIPTION BY DOCTORS

There can no longer be any doubts as to the dangers of Aminophenazone and Dipyrone.

As has been pointed out by *Meyler's Side Effects of Drugs, 90th Edition:* 'Amidopyrine is probably the most dangerous of all anti-inflammatory analgesics. The development of blood dyscrasias after therapeutic doses has been well documented in hundreds of cases. There is no doubt that Amidopyrine has repeatedly been responsible for bone-marrow depression and the death of patients .... The main derivatives of Amidopyrine can provoke the same spectrum of adverse reactions as Amidopyrine itself .... both Amidopyrine and its derivatives are dangerous in the same way and to the same extent.' (Meyler's 1980: 146, 147)

There is therefore an urgent need for the two drugs to be banned.

The only time the drugs should ever be used is as a last resort, when other, less dangerous measures or drugs have been tried and found ineffective. According to *Martindale, Twenty Eighth Edition,* 'The use of Dipyrone is justified only in serious or life-threatening situations where no alternative antipyretic is available or suitable' (Martindale 1982: 251).

In advertisements of the drugs as well as in the package, labels and information inserts, very strong warnings should be given that the drugs are to be used only for life-threatening diseases. Full contraindications should also be given, and these should be prominently and boldly displayed.

At present, these criteria are not fulfilled by the drug companies. As can be seen in *DIMS*, only the barest information is given on contraindications. Instead, in their advertisements, the drug companies have been highlighting all the wonderful uses of the drugs. The advertisements are therefore irresponsible in two ways:

- They promote the drugs for minor ailments that are not life-threatening at all.
- They do not give enough facts on the enormous risks involved in using the drugs, and the adverse side effects that may arise.

As a result of the scant information provided by drug companies, there is a strong possibility that doctors themselves may not be aware of the side effects of the drugs that they are giving out. For instance, CAP interviewed the Executive Director of Waleta company (a pharmaceutical distributor) in 1982. He told us that BUSCOLYSIN COMPOSITUM, a preparation containing Dipyrone, was formulated by Beacons Chemical Company in Jurong, Singapore. When asked whether doctors were informed about the side effects of Dipyrone, he replied, 'Doctors already know of the side effects as they have six years of medical training - they will know.'

CAP also asked whether doctors were given further information

about the drug and was told, 'We are not to teach doctors, they know better. A doctor uses the drug at his discretion. We cannot control them.' According to him, 'Doctors generally do not check whether patients are hypersensitive to the drug.'

When CAP informed him that the drug, which has been banned in many countries, is not a simple drug and should not be given for trivial complaints like menstrual pain, he replied, 'This drug is legitimate and the government has not banned it in Malaysia. There is nothing to prevent us from selling the drug and we have a right to sell it. The risk is the patient's.'

In government hospitals, there is evidence that Dipyrone is given out to women with menstrual pains. This was confirmed by some CAP staff who, in 1983, visited a government hospital in Penang with the complaint and were prescribed BARALGIN, a preparation containing Metamizol.

In another case, a doctor in Butterworth prescribed BUSCOLYSIN COMPOSITUM for a man with headache. The man became mentally unbalanced for a while, not because of Dipyrone but because of some other drug simultaneously prescribed; however, it does prove that Dipyrone is given for such minor complaints as headaches.

More evidence that Aminophenazone and Dipyrone are used by doctors for treating very minor ailments is seen in the cases cited in the previous chapter, where the drugs are prescribed for abdominal pain, cough, cold and fever. What is especially unforgivable is the administration of the drugs to children, when the 'recent increase in the use of Dipyrone in cases of

agranulocytosis and death resulting from it must give us pause, particularly since so many children are among the victims' (Huguley, C.M. 1964: 938-41).

The Philippine Paediatric Society has been warning paediatricians that Dipyrone is highly protein bound, so it takes at least 15-20 minutes to take effect, even after intramuscular injection (Ang Mamimili 1979 Vol VII No. 11: 166-7). This means that it stays in the body longer, hence detoxification is delayed and this condition is very dangerous to children.

As admitted by a paediatrician CAP interviewed, one reason why the BONPYRIN brand of Dipyrone is widely used by doctors is that it is very cheap.

Therefore we can see that the drugs, especially Dipyrone, are widely used because of three major factors:

- the price, which is low considering the potency of the drugs;
- unethical advertising recommending the drugs for a wide variety of ailments, including minor ones, and even for use among children;
- incomplete contraindications given for the drugs, and inadequate information regarding the dangers of the drugs.

CHAPTER 13

CONCLUSION

This report has attempted to make a case for the need to remove all Aminophenazone and Dipyrone preparations from the market. In so doing it has examined current studies on both drugs in the literature, legislation and action taken by health authorities on the drugs worldwide; the dubious marketing practices of drug companies in some Third World countries; and information and marketing of both these drugs in Malaysia.

Aminophenazone and Dipyrone, as has been clearly shown, are two very potent and extremely toxic drugs. Given the availability of alternative anti-inflammatory agents on the market today, which are just as effective and without some of the lethal side effects associated with both these drugs, it is clear that these drugs should not be in use. They have been shown to be unpredictable and dangerous and hold no real advantage over other presently available preparations. It would be worthwhile to quote once more the dangers of both these drugs according to *Meyler's Side Effects of Drugs, 90th Edition:* 'Amidopyrine is probably the most dangerous of all anti-inflammatory analgesics. The development of blood dyscrasias after therapeutic doses has been well documented in hundreds of cases. There is no doubt that Amidopyrine has repeatedly been responsible for bone-marrow depression

and the death of patients .... There is no indication why Amidopyrine should not be replaced by other analgesic or anti-inflammatory drugs .... The main derivatives of Amidopyrine can provoke the same spectrum of adverse reactions as Amidopyrine itself .... both Amidopyrine and its derivatives are dangerous in the same way and to the same extent .... There can be no doubt that Amidopyrine and Dipyrone cause agranulocytosis .... Since effective, less dangerous alternative drugs are available there is no case for the continued use of Amidopyrine and Dipyrone' (Meyler's 1980: 63-4;146-7).

A disturbing feature found in this study is that drug companies practise double standards in the marketing of Aminophenazone and Dipyrone in Malaysia (a developing country) as compared to developed countries.

From a detailed analysis of the information supplied by the drug companies in *DIMS* and the comparison of information in the drug inserts of Aminophenazone and Dipyrone products sold in Malaysia, it can be seen that drug companies are irresponsibly promoting their products in Malaysia. In the drug inserts, the 'Indications' given range from sprains and headaches to colic and dysmenorrhoea. Conversely, under 'Contraindications', the conditions in which the drugs cannot be used are either narrowed down or entirely excluded. Much of the important information which should be included in the 'Contraindications' and 'Warnings' and 'Precautions' are instead casually mentioned under a 'Note'. The information given deliberately plays down the dangers of the drugs. The dangers of serious or lethal side effects are deliberately minimized, glossed over, or even totally ignored.

Children have been found to be most susceptible to the adverse effects of the drugs. In 1964, the *JAMA* reported that many children had been made victims of Dipyrone-induced agranulocytosis. In the 1970s, surveys in Finland have shown that 50% of the cases of Aminophenazone-induced reactions ended fatally and children were found to be as vulnerable as adults. Hence it can be seen that both these drugs pose a real danger when used in children. Yet drug companies in Malaysia are promoting Dipyrone preparations for children in the form of injections, tablets, syrup and drops. These include BARALGIN (Hoechst), CONMEL (Winthrop), DEPARON (Westmont) and NOVALGIN (Hoechst).

Drug companies cannot be allowed to promote such a potent and toxic drug for such minor conditions. This kind of promotion can lead to irrational drug prescribing and drug use, and to needless injury or death. From the above discussion, one can see that drug companies have been indulging in most unethical, aggressive double-standard marketing of their drugs. This is tantamount to the relegation of moral and social responsibility. Aminophenazone and its related derivative, Dipyrone, as very explicitly stated in the medical literature, should be promoted only for life-threatening conditions where other less toxic drugs have failed to be effective.

CAP strongly urges the Ministry of Health to recall the drug from the market immediately, for the safety and health of Malaysian consumers.

It is evident that multinational drug companies adopt lax double-standards in their marketing precisely because there are no mandatory requirements for them not to do so. Any information they divulge regarding their products is at present on a 'voluntary basis' or 'what the law of the country requires' and this is simply not good enough and can be disastrous. Thus a 'watchdog' committee is urgently required to help promote awareness and corporate responsibility.

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f) - 'Other Recent Regulatory Decisions', April-June 1979: 13

g) - 'Other Recent Regulatory Decisions', October-December 1979: 16-7

h) - 'Other Recent Regulatory Decisions', October-December 1980: 22

i) - 'Other Recent Regulatory Decisions', January-December 1983: 23, 29

j) - 'Other Recent Regulatory Decisions', January-March 1984: 26

APPENDIX 1

HOECHST (MALAYSIA) MEMO ON DIPYRONE

Hoechst

Hoechst Malaysia Sdn. Bhd.
P.O. Box 540, Kuala Lumpur
Telephone 987056
Telex K. Lumpur Hoe Ma 30370
Cable Hoechst Kualalumpur

Head office 468-6C, Jalan Ipoh, Kuala Lumpur
Penang Sales Centre 49 Weld Quay, P.O. Box 501
Penang Tel. 24342, 22234
Kota Bharu Sales Office 11200 Jln Padang Garong
Ipoh Branch Tel. 21330
Kuching Sales Centre 305, Padungan Road
Kuching Tel. 31102, 31103, 31141
Johore Bharu Sales Centre 228-A, Jln Tun Abdul Razak
P.O. Box 34 Johore Bharu Tel. 21060, 24192

Young Newton & Partners
4, Jalan Ampang

Kuala Lumpur

Attention: Dr. L.K. Tee
Mr. Pillay

Your Ref	Your letter dated	Our Ref	Kuala Lumpur
		KF-jo	27th January 1982

Dear Sirs,

We like to refer to the discussion in your office on 24th December 1981 between your Dr. Tee, Mr. Pillay and the left undersigned. As promised, we like to give you a short write-up of our discussion.

We agreed that the subject of mild analgesics has internationally been under consideration during the past years and unfortunately also a lot of misleading information was circulated. Mild analgesics like dipyrone are being used since a very long time (1922) and extensively. The most widely used compounds/combinations are ASA - paracetamol and phenacetin - dipyrone and propyphenazone. The international consumption of these analgesics varies. Whilst phenacetin in the majority of countries has been banned, the main use of ASA lies in North America. Paracetamol is widely used in Scandinavia, UK and Asia. Dipyrone and propyphenazone are mainly used in Continental Europe, Asia, South America and Africa.

Though all these compounds are proven worldwide, they differ in potency. (It should be stressed that dipyrone is equipotent to pethidine). It is known that all these analgesics may in rare cases cause adverse reactions however with different mechanisms. ASA can cause major gastrointestinal bleeding, renal damage and asthma. Paracetamol can produce irreversible liver damage. Dipyrone and propyphenazone may in very rare instances induce immunological reactions in the granulopoetic system. Regarding the rare side effect of agranulocytosis statistics from the FDA, USA for the years 1969 - 1976 show that 207 various drugs are allegedly associated with this side effect. Please refer to enclosure I listing the first 10 products associated with agranulocytosis in the U.S. It might be that as the first suspected incidence was seen in connection with pyrazolone in 1912, it is since then under more critical observation than any other compound and still the likelihood of such side effect remains extremely rare. (Estimated to be 1 - 2 per million). Because of the rarity of the event and the presence of background of spontaneous instances of such events, it is very difficult to establish the causal relationship if any.

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To quantify the risks of drug induced agranulocytosis of all drugs, an international study is being conducted since 1978 by the drug epideminological unit, Boston University, USA, on a worldwide basis comprising of a population of some 30 million people. In view of rarity of cases, this study is expected to be completed end 1983 only.

Considering that Baralgin besides its very effective oral presentations is one of the most widely used parenteral spasmolytics given by intravenous routes and found to be very effective in even severe spasms over and above non-narcotics, there is no doubt regarding its usefulness for the medical practitioner. The very rare occurence of hypotensive episodes is no greater than that found with other I.V. injections.

You specifically requested to receive a picture on the worldwide situation in view of where dipyrone is not available. In this respect, please refer to enclosure II.

Also the Federal Health Office in Germany (BGA) follows closely the world wide dialogue concerning mild analgesics. In June 1981 the BGA organised a special session to discuss the question of risks/benefits ratio, starting with the pyrazolone group of compounds. After thorough discussions among clinicians, haematologists, epidemiologists and clinical pharmacologists, the BGA summarized the findings. In December 1981 the President of the BGA declared in front of journalists that one should monitor the possible abuse of analgesics in general and should try to educate the population that drugs should only be taken when really indicated and when given over a longer period of time this should be done under medical supervision. If such rules would be followed he predicted a positive benefit/risk ratio. He emphasised that this is valid for all analgesics available, including pyrazolone derivatives. In connection with the pyrazolone group of compounds, being the first one studied, he stressed that all those derivatives would remain available to the medical profession though there would be a restriction of unjustified combinations, e.g. with corticosteroids. A consideration would be to put them (metamizol, isopyrin and propyphenazone) under prescription which seems the best way to minimise their abuse. Furthermore in line with acceptable practice, appropriate labelling for prescription drugs would be proposed.

The negotiation between the experts in the BGA and the pharmaceutical companies during the next months aim at defining the proper use of analgesics. Our company has since many years included comprehensive information for the physician and patient in the text of the packing and inserts of our relevant products and we are therefore already now in line with the future request from the BGA in Germany. It might furthermore be of interest that in Germany itself the number of pyrazolone compounds increased to 1,400 drugs during the last 10 years and that they are still available without prescription.

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Hoechst

Addressee
Young Newton & Partners

Our Ref. KF-jo

Date 27.01.82

We hope that the above information will answer the questions forwarded and will convince you on the basis of objective and factual data.

Yours faithfully,
HOECHST-MALAYSIA SDN. BHD.

M. Friederich K.E. Chan

continued next page

Encl. I

Abstract of USA Food and Drug Administration report, ref. 09/15/76, identifying 207 products associated with 586 reported cases of agranulocytosis for the period of 1969 to 1976. The first 10 products extracted according to number of reported reactions are :-

Mellaril	62	reactions
Thorazine	35	reactions
Butazolidin	33	reactions
Pronestyl	26	reactions
Tanderil	16	reactions
Keflin	14	reactions
Valium	14	reactions
Tofranil	14	reactions
Azulfidine	12	reactions
Dilantin	12	reactions

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SITUATION WORLD-WIDE

Dipyrone was banned in Australia in 1965. Though the Australian Ministry suspected dipyrone to be the main cause of agranulocytosis it was proved by Government statistics that after the ban of dipyrone the incidence of this side-effect did not decline as can be seen below.

Incidence of agranulocytosis in Australia

Year	Incidence of agranulocytosis per 100,000 population
1963	0.05
1964	0.05
1965	0.06
April 1965	pyrazolone banned
1966	0.06
1967	0.05
1968	0.08
1969	0.03
1970	0.07
1971	0.04
1972	0.05
1973	0.02
1974	0.09

In Sweden the ban was imposed in 1974. BOTTIGER et al, who at that time recommended the ban later commented in 1979 after being confronted with Government statistics "This could be taken as an indication that individual susceptibility plays an important role, more important perhaps than the offending drug. In other words at least at a low degree of exposure to sensitizing drugs, a number of sensitive individuals will develop negative reactions to a variety of drugs".

...2/-

continued next page

In USA, dipyrone was banned in 1976. This was on the basis of 13 cases of agranulocytosis observed over a period of 10 years. However the observation was not based on sound scientific methodology and was severely questioned in 1979 during the International Conference on Mild Analgesics.

The remaining countries where dipyrone was banned are:

Singapore (1978) - reasons unknown (no statistics available)
Denmark (1979) - under hearing (no statistics available)
Jordan (1979) - reasons unknown (no statistics available)
Saudi Arabia (1980)- reasons unknown (no statistics available)

In all other parts of the world, pyrazolones including dipyrone are available after its launch in 1922 with the exception of Uk and Canada where it was never introduced.

APPENDIX 2

DRUG INFORMATION INSERT FOR BONPYRIN

BÖNPYRIN

Antipyretic and Analgesic

Description

Bonpyrin, brand of sulpyrin J.P., chemically sodium methylaminoantipyrinemethane sulfonate, is one of the most effective preparations among antipyrine derivatives for fever and pains.

The injection is a 25% or 50% aqueous solution, and the tablet contains 0.5 Gm. of the compound.

Indications

Headache, pain of muscular and articular rheumatism, lumbago, sciatica, polyarthritis, myositis; Influenza and other febrile condition.

Administration and Dosage

Orally: Usually 1 to 3 tablets a day in divided doses.

Parenterally: Usually 2 to 4 ml. of 25 % solution or 1 to 2 ml. of 50 % solution, 2 to 3 times a day subcutaneously or intramuscularly.

If intravenous injection is desirable, 1 ml. of 25 % solution once or twice daily at first, the dose is then increased to 4 ml. a day.

Caution

1. Sulpyrin may cause agranulocytosis.
2. Store away from light.

Packages

Tablets	(0.5 Gm.)	20, 100 and 1,000 tablets in bottle.
Injection	(25 %)	2 ml. 10 and 50 ampules in carton.
	(50 %)	2 ml. 10 and 50 ampules in carton.

TAKEDA CHEMICAL INDUSTRIES, LTD.

27, Doshomachi 2-chome, Higashiku, Osaka, Japan.

APPENDIX 3

DRUG INFORMATION INSERT FOR BARALGIN

Baralgin®

Spasmolytic and analgesic

Composition

	Sodium phenyl-dimethyl-pyrazolone-methylamino-methanesulphonate (metamizol)	4'-(β-Piperidino-ethoxy)-benzophenone-carboxylic acid-(2)-methylester hydrochloride (pitofenone hydrochloride)	2,2-Diphenyl-4-piperidino-butyramide-bromo-methylate (fenpiverinium bromide)
Injection solution (1 ml)	0.5 g	0.002 g	0.00002 g
1 Tablet	0.5 g	0.005 g	0.0001 g
1 Dragée	0.25 g	0.0025 g	0.00005 g
Drops (1 ml)	0.5 g	0.005 g	0.0001 g

Properties

Baralgin contains the analgesic and spasmolytic sodium phenyldimethyl-pyrazolone-methylamino-methanesulphonate (metamizol) and a papaverine-like substance, 4'-(β-piperidino-ethoxy)-benzophenone-carboxylic acid-(2)-methylester hydrochloride, as well as a parasympatholytic component, 2,2-diphenyl-4-piperidino-butyramide-bromo-methylate.

The pharmacological properties of these three components render Baralgin particularly suitable for the relief of painful smooth muscle spasms, since beside a prompt and prolonged analgesic effect it brings about relaxation of the spasmodically contracted smooth muscles by its direct action on the muscle cell and inhibition of cholinergic impulses.

Indications

Spasms of smooth muscles such as ren...l colics, ureteral spasms, vesical tenesmus, biliary colics and dyskinesias, gastrointestinal spasms. Spastic dysmenorrhoea. Migrainous headache.

Dosage and administration

In acute, severe colics, 5 ml (1 ampoule) of Baralgin is injected slowly intravenously (duration of injection, 5 – 8 minutes). This dose may be repeated 6 – 8 hours later, if necessary. After intramuscular injection the onset of action is delayed by 20 – 30 minutes.

For after-treatment and for treatment of mild to moderate pain, spasms or tenesmus, the use of drops, dragees or tablets is advisable.

Unless otherwise directed by the physician, the following dosage guide is recommended.

Daily dose	Tablets	Dragées	Drops
Adults	3 × 1 – 2	3 – 4 × 2 – 3	3 – 4 × 20 – 40
School children	3 × ½ – 1	3 × 1 – 2	3 – 5 × 10 – 15
Younger children	–	–	5 – 6 × 3 – 5 – 8
Infants over 4 months	–	–	5 – 6 × 3 – 5 – 8

Before using the drops, note:

After unscrewing the cap, hold the bottle at an angle with the opening pointing downwards and lightly tap the bottom of the bottle with a finger to initiate dropping if necessary.

Side effects

Central nervous symptoms of a non-allergic origin, such as vertigo and a feeling of oppression, may occur especially after too rapid intravenous injection. Therefore the period of time recommended for the injection should be strictly observed.

The said side effects can be largely avoided by slow injection. Baralgin contains metamizol, a pyrazolone derivative that may occasionally produce hypersensitivity reactions in the form of skin changes or reduced blood leukocyte count or, in very rare cases, agranulocytosis. Therefore this preparation should be discontinued and medical advice should be sought if unusual indispositions or changes of skin or mucosae are observed.

Symptoms of shock, which may be the manifestation either of an anaphylactic reaction or of too rapid injection, always necessitate an immediate interruption of the injection and prompt countermeasures, such as putting the patient in a lateral position, ensuring free airways, artificial respiration, catecholamine administration (noradrenaline, adrenaline, orciprenaline), high doses of corticosteroids, continuous intravenous drip.

In case of **overdosage** convulsions may occur, especially in children. To remove Baralgin from the stomach, vomiting should be induced and gastric lavage carried out. If necessary, sympathomimetic drugs may be given in small doses.

Provided the patient's consciousness is not clouded, vomiting is induced in the following way: Adults are made to drink quickly ¾ – 1 litre of warm salt water (1 – 2 tablespoonfuls of salt dissolved in one glass of water). This procedure is repeated until clear liquid is vomited. Small children in their 1st – 6th year are given as much as possible of some warm fruit juice.

The elimination of already absorbed metamizol can be stimulated by forced diuresis or dialysis. At the same time the heart, circulation and respiration must be monitored and, if necessary, supported by drugs. Artificial respiration may be required. In the presence of convulsions, rapid-acting barbiturates or diazepam are to be injected without delay.

continued next page

Contraindications

Pyrazolone allergy, granulocytopenia, acute intermittent porphyria.

States of collapse, severe cardiac failure, tachyarrhythmia, coronary insufficiency, glaucoma, hypertrophy of the prostate with a tendency to residual urine, mechanical obstruction of the gastrointestinal tract, megacolon.

Please note

Without the doctor's instructions this preparation should not be taken in high doses or for prolonged periods of time.

Intravenous injection must be given slowly, at a rate of about 1 – 1,5 ml per minute.

Before the injection the patient must be questioned about a history of pyrazolone allergy.

During pregnancy, especially the first three months, drugs should be used only if strictly indicated. If pregnancy is suspected, the physician must be consulted about further use of Baralgin.

If employed in the usual therapeutic doses, pyrazolones enter the breast milk in small amounts only.

Infants less than 4 months old must not be given Baralgin.

Baralgin generally does not cause drowsiness. However, alcoholic beverages should not be consumed simultaneously since Baralgin may increase the effect of the alcohol.

Baralgin is incompatible with indigo carmine and therefore must not be mixed with it in the syringe.

A harmless phenomenon is the reddish coloration of the urine after Baralgin administration. It is due to the elimination of rubazonic acid, a pyrazolone metabolite.

Presentation

3, 5 and 25* ampoules of 5 ml
Vials of 10 ml injection solution
20 and 250* tablets
20 and 250* dragees
10 ml of drops (dropper bottle)

* Hospital packs

Amaran: Ubat ini mungkin mengakibatkan »agranulocytosis« yang membawa maut.

Hoechst AG · Frankfurt am Main
Germany

Hoechst

POKF – G 33 – 01 008/2

APPENDIX 4

DRUG INFORMATION INSERT FOR BENZA FORTE

BENZA FORTE Tablets

Combination of cold remedies and vitamins

Description

Benza Forte is a cold tablet made according to a fortified formula and containing the following ingredients in each tablet. It possesses a marked effect in the treatment of various types of colds.

Tripelennamine hydrochloride	25 mg.
Metamizol	40 mg.
Phenacetin	50 mg.
Ethoxybenzamide	150 mg.
Caffeine	50 mg.
Codeine phosphate	5 mg.
Hesperidin methyl chalcone	15 mg.
Vitamin C	70 mg.
Ephedrine hydrochloride	5 mg.

Indications

Common colds (especially accompanied by cough and fever), coryza, influenza, headache, toothache, pain following dental surgery.

Administration and Dosage

One tablet, 3 times daily, with suitable liquid between meals.

Precautions

1. Drowsiness may occur in sensitive patients.
2. Caution is required in individuals sensitive to antipyrine derivatives.
3. Should not be used for infants below 6 years old.

Packages

Sugar-coated Tablets: Packet of 6
Bottles of 100 and 500.

TAKEDA CHEMICAL INDUSTRIES, LTD.

27, Doshomachi 2-chome, Higashiku, Osaka, Japon.

EFT 1

ベンザホルテ(英タイ仏文)

APPENDIX 5

DRUG INFORMATION INSERT FOR SISTALGIN COMPOSITUM

Sistalgin comp.

Antispasmodic + Analgesic

. MERCK

Sistalgin comp. combines the potent antispasmodic and analgesic actions of pramiverine and metamizol.

Indications

Painful spasm and colic, in the following clinical situations:

Gastro-intestinal tract, gastro-duedenitis, post-gastrectomy syndrome, peptic ulcer, irritable colon, etc.

Biliary tract, biliary dyskinesia, cholelithiasis, etc.

Urinary tract, urethritis, cystitis, irritable bladder, renal calculi, etc.

Gynaecological disorders, spasm associated with dysmenorrhea, etc.

Post-operative pain, following catheterisation and a wide variety of surgical procedures.

Adult dosage

Dosage with Sistalgin comp. depends on the intensity of the pain. Relief is usually obtained at the following dosage levels.

Ampoules Single dose in acute cases, 1 to 2 ampoules, by slow i. v. or by i. m. injection. The daily dose should not exceed four ampoules. By slow intravenous infusion, three ampoules may be added to 5% glucose solution in an infusion time of 8 hours.

Tablets The usual dosage is 1 tablet 3 times daily during meals On the first day, when no ampoules are given, up to 2 tablets three times daily may be given if required.

When treatment is necessary for more then three days, effective control can be achieved at half the above dosages.

Side-effects

Side-effects with Sistalgin comp. are dose related, but at recommended dosage they can be expected to be less frequent and less severe than with other anticholinergic drugs. These include dryness of the mouth, blurring of vision, flushing and dryness of the skin, nausea and mild tachycardia Cases of agranulocytosis have been reported following the use of metamizol in certain predisposed patients.

Contraindications

Sistalgin comp. is contraindicated in glaucoma, prostatic hypertrophy, partial organic pyloric stenosis, and megacolon. Owing to the metamizol content, Sistalgin comp is also contraindicated in acute intermittent porphyria Care should be taken in administration to patients with severe heart diseases and following abdominal surgery

Presentation

Sistalgin comp. ampoules

Each 5 ml ampoule contains pramiverine 2 25 mg and metamizol 2500 mg

Boxes of 5 ampoules

Sistalgin comp. tablets

Each coated tablet contains pramiverine 2 mg and metamizol 250 mg

Bottles of 100 and 1000 coated tablets

Sistalgin: Trade Mark

E. Merck, Darmstadt F.R. Germany

A 5 4 3 2 787 460 1111–0

APPENDIX 6

DRUG INFORMATION INSERT FOR NOVALGIN

Novalgin®

Highly effective analgesic, spasmolytic, antirheumatic, and antipyretic; free from alkaloids

Indications

Various kinds of pain, such as headache, neuralgia, sciatica, lumbago etc. —Biliary and renal colics (in these cases Novalgin injection is often substituted for the usual alkaloids) —Muscular rheumatism and polyarthritis (preferably large parenteral doses). — Influenza and febrile diseases.

Dosage

Tablets and drops:

1—2 tablets 3—4 times daily or 20—40 drops 3—4 times daily In chronic febrile conditions ¼—½ tablet at intervals of 60 minutes.

The tablets are best taken after disintegrating in a little water Novalgin in the form of drops has proved to be particularly useful in pediatrics. Children from 4 months to 5 years are given 2—6 drops 3—4 times daily, older children 10—15 drops 3—4 times daily

The dropper bottle must be held upside down in a vertical (not an oblique) position and shaken slightly After a few seconds the drops will begin to run out

Suppositories:

Adults. 1 suppository of 1.0 g 1—3 times daily

Children over 4 months 1 suppository of 0.3 g. (for children) 1—3 times daily, according to age and the requirements of the case

If the suppositories have lost their original shape through heat, they may be remoulded rapidly and cautiously by hand Before insertion, dip them briefly in cold water

Injection solution

Intramuscular injection The average daily dose is 4—6 ml (= 2—3 g Novalgin) Children from 2—14 years receive 0.5—2 ml The solution should be warmed to body temperature for intramuscular injection

continued next page

Intravenous injection (slowly, about 2 ml per minute) Intravenous injections are particularly indicated in acute polyarthritis and its complications. After an initial dose of approx. 2ml the dosage may, if necessary, be increased to 5ml twice daily Children from 2–14 years are given 0 5–1 ml
In colics and other very painful conditions 5 ml is usually sufficient.

Tolerability
Novalgin is well tolerated However in rare cases it may cause allergic reactions that necessitate discontinuation of the medication
Analgesics should not be taken in high doses or over prolonged periods without consulting the physician.

Presentation
Tablets: 10, 20 and 250* tablets of 0 5 g each
Drops (50%): Dropper bottles of 10 and 20 ml / Bottle of 250* ml
Suppositories: 5 and 25* suppositories of 1 0 g each
5 suppositories of 0 3 g each for children
For injection (50% solution):
10 and 100* ampoules of 2 ml each / 5 and 25* ampoules of 5 ml each
Bottle of 50 ml (with pierceable rubber cap)
Powder: 100* g
* Hospital packs

Hoechst AG Frankfurt (Main)

APPENDIX 7

DRUG INFORMATION INSERT FOR DOLO-NEUROBION

Dolo-Neurobion®

295 engl./thai./chin.

Neurotropic Vitamins + Analgesic

MERCK

1 coated tablet contains:

Vitamin-B_1-nitrate 50 mg; Vitamin-B_6-hydrochloride 100 mg; Vitamin-B_{12}-Cyanocomplex 100 mcg; Metamizol (Phenyl-dimethyl- pyrazolone-methylamino-methane-sulphonate sodium) 250 mg.

The vitamins B_1, B_6 and B_{12} are indispensable for the normal functioning of the nerve cell metabolism. The addition of the analgesic compound metamizol is of particular advantage especially in the presence of severe pain where rapid relief is desired. Therefore, Dolo-Neurobion coated tablets are prescribed in all painful conditions of the nervous system and the spine, as well as to support parenteral therapy started with Dolo-Neurobion ampoules, on days without injection and for the prevention of relapses.

Dosage:

Unless otherwise prescribed by the physician, 3 times daily 1–2 coated tablets. On days where Dolo-Neurobion is administered parenterally, the dosage may be reduced to 2 times daily 1 coated tablet.

Note:

Dolo-Neurobion is well tolerated. In rare cases, however, a sensitization due to metamizol may occur and require discontinuation of therapy.

Presentation:

Bottles of 100 and 1000 coated tablets

Also available:

Packs of 60 ampoules

E. Merck, Darmstadt, F. R. Germany

151 830 G

787 295 1111-1

APPENDIX 8

DRUG INFORMATION INSERT FOR DOLO-ADAMON

Attention read carefully!

Dolo-Adamon®

Against severe pain and spasm

Composition:	Injection (1 ml.)	1 ctd. tablet	1 supp.
Ciclonium bromide	5 mg.	10 mg.	20 mg.
Sodium phenyldimethyl-pyrazolonemethylaminomethane sulphonate (Noramidazophen)	500 mg.	250 mg.	800 mg.
Codeine phosphate		14.4 mg.	28.7 mg.
Crbtarbital		50 mg.	75 mg.

Properties: Quick and reliable relief from severe painful conditions, e. g. due to smooth muscle spasm. Long-lasting effect. May replace opiates.

Indications: All severe painful conditions (e. g. colics of the biliary ducts, the urinary passages, bladder tenesm, ulcer pain, dysmenorrhoea); postoperative and post-traumatic pain, neuralgia (e. g. sciatica, slipped disc), migraine, pain occurring within the ear, nose, and throat region, myalgia, tumour pain, parturition (i. v.). etc.

Dosage: If not otherwise prescribed by the physician:
Injection: patients below 70 kg. of body weight 2 ml., patients above 70 kg. of body weight 5 ml., either i. m. or **i. v. slow injection (1 ml./min.) to the recumbent patient.**
Coated tablets: 1 - 2 tablets two or three times daily
Suppositories: 1 suppository two or three times daily
Dolo-Adamon should not be given to children.

Side-effects: Dryness of the mouth, blurred vision. In case of i. v. injections, fall in blood pressure, tachycardia, urinary retention.
In very sensitive patients, Dolo-Adamon may lead to allergic skin reactions, very rarely to granulocytopenia. Pharyngitis may by the first symptom of a beginning granulocytopenia; in such a case the patient should contact the attendant physician.

Contra-indications: Glaucoma, adenoma of the prostate with urinary retention, mechanical stenoses within the gastro-intestinal tract, megacolon, allergy to pyrazolones, granulocytopenia, porphyria, – respiratory depression (ctd. tablets and suppositories only).
I. v. injection: Dolo-Adamon should be used with caution in patients with myocardial disease, coronary incompetence, irregular action of the heart.

Attention: Car and machinery drivers should bear in mind that Dolo-Adamon may induce drowsiness; this applies to an even larger extent to the combination with alcohol.

Presentation: Ctd. tablets: Packs of 20 and 200
Suppositories: Packs of 5 and 50
Injection: Packs of 20 and 50 ampoules of 2 ml.
Packs of 2, 5 and 50 ampoules of 5 ml.
The list of presentation forms is not complete, and all mentioned packs are not available in all countries.

Store drugs carefully! Keep out of children's reach!

APPENDIX 9

DRUG LABELLING FOR CONMEL

APPENDIX 10

DRUG LABELLING FOR BUSCOLYSIN COMPOSITUM

1000 dr. _ es

Buscolysin compositum

Spasmolyticum

[redacted]

Composition

Each dragee contains 10 mg Hyoscine-N-butylbromide and 250 mg dipyrone (sodium phenyldimethylpyrazolone-methylaminomethane sulfonate).

Administration and dosage

Sugar coated tablets: For oral administration to relieve spastic pain in disorders of the gastrointestinal, renal, and female genital tracts, and also in dysmenorrhoea.

Dose: 1–2 tablets, if necessary 3 times a day until pain is relieved. The tablets should be swallowed whole.

6151

WALETA MALAYSIA SDN. BHD.
[redacted], PETALING JAYA, SELANGOR.

Mode of action

Buscolysin (Hyoscine-N-Butylbromide) has a selective antispasmodic action on the smooth muscle of the gastro-intestinal, biliary and urogenital tracts. It has the great advantage that it is virtually free from the side effects usually associated with drugs of the atropine series.

Dipyrone which exerts analgesic and spasmolytic action increases the spasmolytic effect of Buscolysin.

Buscolysin Compositum is a combination of Buscolysin with dipyrone. It is used for the relief of colic and severe spastic pain in conditions in which an analgesic as well as an antispasmodic effect is required.

Indications

Acute spastic spasms of the gastrointestinal tract. Biliary colic, renal colic and other conditions of paroxysmal abdominal pain.

Painful spastic conditions of the female genital system; dysmenorrhoea.

Contraindications

Children under 12 months of age should not be given Buscolysin Compositum, but only the plain Buscolysin without dipyrone. Although dipyrone is a soluble and generally well tolerated aminopyrine derivative, as with all derivatives of this group, prolonged administration is inadvisable, particularly in patients with a history of drug allergy on blood dyscrasia.

6v-23-3@ Rs. 25/- S/117

Drugs and the Third World:

Aminophenazone and Dipyrone Hazards and Marketing Practices

Aminophenazone and Dipyrone are two extremely toxic painkilling drugs which have caused great suffering and even death among their users. Their known adverse side effects have prompted many countries to ban or severely restrict their use.

In Malaysia, however, the two drugs are easily available and indiscriminately used.

This report shows that such a dangerous situation exists because of laxity on the part of the Ministry of Health, thus allowing the multinational pharmaceutical companies to get away with unethical marketing practices.

The Consumers' Association of Penang (CAP) is a non-profit making organisation which fights for the rights and interests of Malaysian consumers through research, educational and representational activities.

The issues it takes up include the fulfilment of basic needs (food, nutrition, health, housing, transport, etc.), food and product safety, environmental pollution and problems, the rational use of resources, specific problems of women, and business malpractices.

This is part of a series of CAP Reports aimed at providing the public with the results of some of the important areas of CAP's activities. It is hoped that this series will generate public interest and awareness, and help to contribute towards a better life for Malaysians.

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